American Journal of Digestive Diseases

Volume 16

The American Journal of

DIGESTIVE DISEASES

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DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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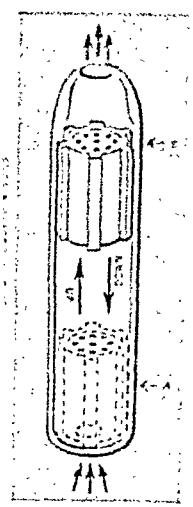
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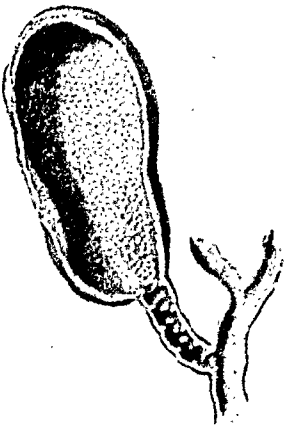
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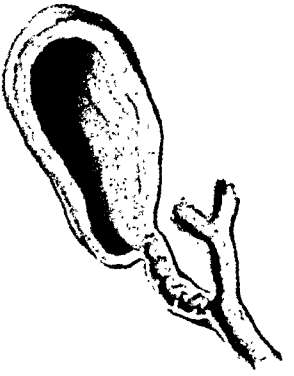
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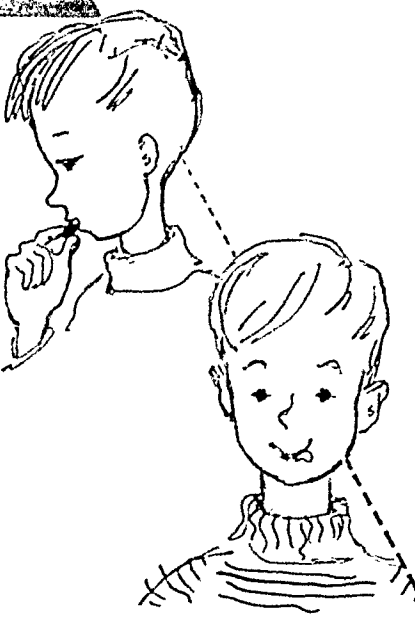
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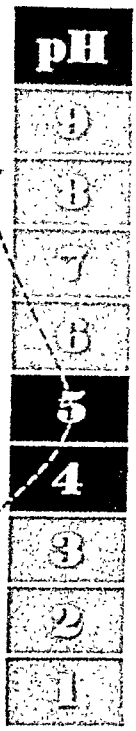
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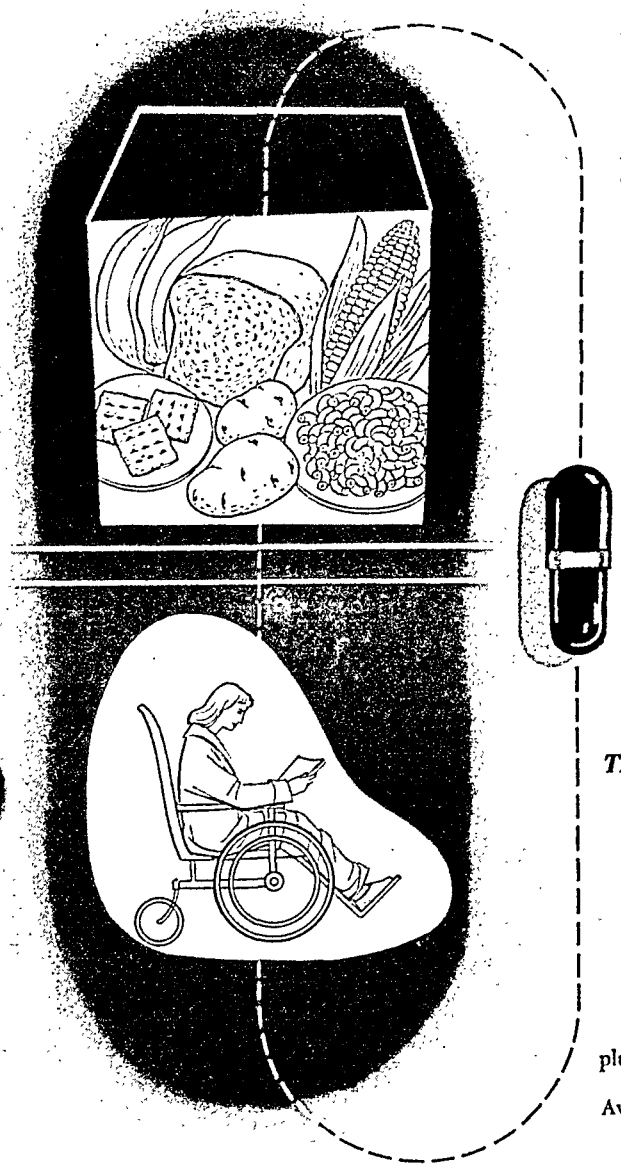
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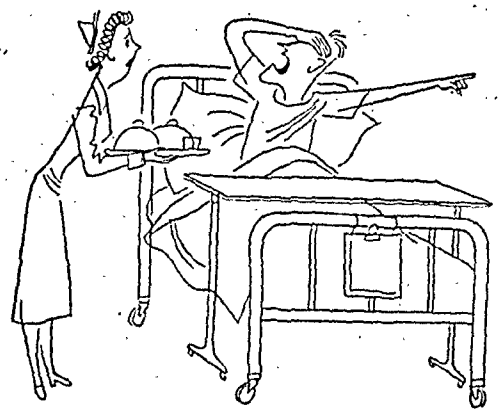
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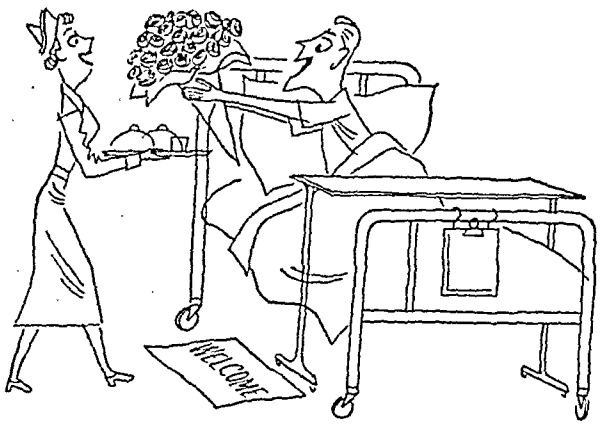
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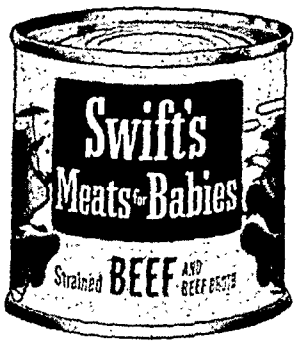
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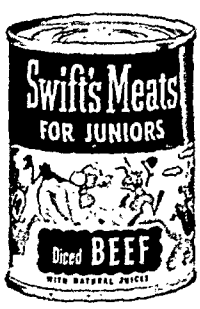
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Every growing child needs a diet balanced as to calorie, protein and vitamin requirements. But, often, a theoretically correct diet may actually be vitamin deficient. For instance, the child may eliminate habitually certain foods; or digestive disturbances may interfere with assimilation. Improper or excessive cooking also will dissipate certain vitamins. A continued mild vitamin deficiency can result in fatigability, irritability, skin eruptions, susceptibility to colds and infections.

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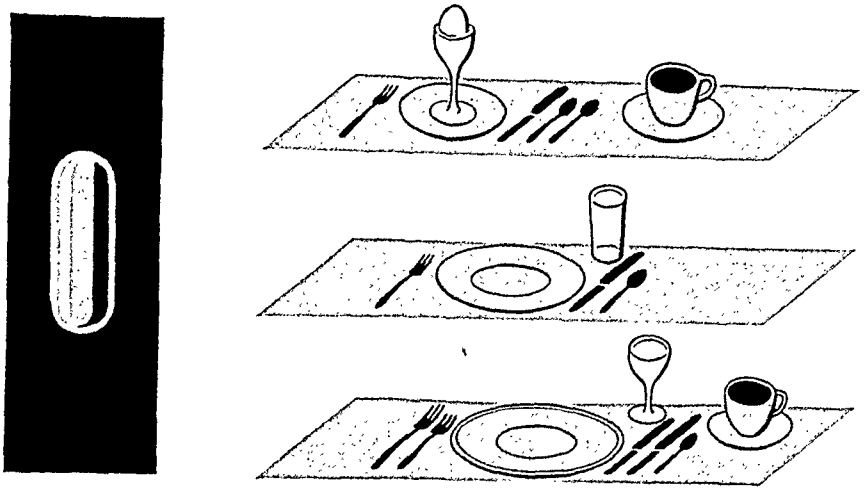
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A Critique on Vagotomy, Part II: The Contemporary Use of Vagotomy

By

W. J. MERLE SCOTT, M.D.

and

JOHN A. SCHILLING, M.D.

In Part I the experimental and clinical background of vagotomy was outlined. From this it is seen that the basic physiological results of vagotomy in animals had been fairly well established but with many conflicting conclusions and important gaps in our knowledge. Also sporadic attempts to apply this information to the treatment of human disease has been made in many parts of the world. But the choice of cases and the analysis of results were inadequate to establish definitely the clinical value of this procedure. In 1943 Dragstedt and his associates at the University of Chicago reported the first accurately controlled clinical investigation of vagotomy in the treatment of duodenal ulcer. Since that time in successive reports the course and findings in these and additional patients has been presented. This clinical use of vagotomy was based upon his concept, derived from years of independent investigation, concerning the physiology of the upper gastro-intestinal tract. Shortly thereafter, Moore and his colleagues at the Massachusetts General Hospital and Grimson and his associates at Duke University began the critical study of this problem. More recently other clinics have also taken up this investigation. Because of the care with which they have been studied, and the period of observation these series of patients provide us with data to judge not only the immediate but also the intermediate results of vagotomy in the treatment of peptic ulcer. Recently this procedure has been taken up enthusiastically in many parts of the world, and now a widespread uncritical adoption of vagotomy threatens to delay the ultimate evaluation of its usefulness. Only the test of time will provide this. Vagotomy is not a panacea.

A. *Immediate Results*

Pain: All reports are in agreement that the most obvious immediate clinical result of vagotomy is a dramatic relief of pain. When present in an acute form before operation, the patient is usually aware of its absence on recovery from anesthesia. Recurrence of spontaneous ulcer — mimetic pain has been observed in all of the series, but only in a minority of the cases (see complications and failures). Furthermore, ulcer niches demonstrated before operation usually disappear within a few weeks after operation, along with the evidence of spasm in the duodenal cap, but the fixed deformity of the cap if present usually remains.

Motility: Also all investigators agree that there is a marked effect on the motility of the stomach after complete vagus denervation. However, this is observed both by clinical and mechanical methods in greatly varying degrees. Rhythmic contractions of the stomach are not abolished but regularly show a decrease. By X-ray the stomach may have the appearance of an atonic sac and gastric retention even to 24 hours or longer may be found. However, in many patients peristalsis is active, though the vagus denervation of the stomach is apparently complete. For details concerning the post operative motility of the stomach graphic studies may be found in reports by Dragstedt, Grimson and Moore with their associates.

Secretion: Gastric secretion is affected both in total quantity and in its constituents. The excessive amounts of acid that characterize the secretory activity of the stomach during the active phase of a duodenal ulcer usually decrease to the normal range. The large night volume which is frequently found before operation diminishes rapidly. The secretory response to insulin has been advocated as a test of the completeness of the vagotomy. There are serious defects in the clinical use of this test as such a criterion. And it is certainly not true that vagus denervation of the stomach prevents all acid secretion. However, any patient who in response to insulin secretes abnormally large amounts of acid probably has some intact vagus secretory fibers to the stomach. The secretion of pepsin is probably also decreased after vagotomy though to a considerably lesser degree than that of hydrochloric acid, while the amount of mucus elaborated by the stomach seems little affected. The pepsin studies have been much less frequently carried out than the acid studies. And the methods for mucus determination are too inadequate for any certain conclusions to be drawn from such studies. In addition to these effects on gastric secretion there are quite surely changes in the function of other secretory cells. The external pancreatic secretion seems to be considerably altered both in its total amount and in its constituents. As yet the effect on the liver and the small intestine as secretory organs has not been carefully investigated but presumably important changes may be found here also.

Complications: Two significant complications have arisen to affect the immediate results, viz., (a) gastric stasis, and (b) diarrhea.

From The Department of Surgery, The University of Rochester School of Medicine and Dentistry, Rochester, New York.

Submitted August 31, 1948.

Gastric Stasis: Most patients whose food leaves the stomach through an intact pylorus after vagus denervation have some demonstrable gastric stasis. Frequently symptoms due to the latter are present for some weeks and sometimes for many months. The clinical manifestations vary from a mere sense of fullness to vomiting and distension suggesting an almost complete obstruction. The most frequent complaints after vagotomy are attributable to gastric stasis and include eructations, pyrosis, inability to gain weight or strength, bloating, etc. Fortunately in the majority of instances these symptoms in any severe form are a passing phase and disappear entirely or are greatly ameliorated within a few weeks. It is surprising how little disturbance may be caused by gastric stasis proven by X-ray to be present, even to 12 or 24 hours. All series, however, include several cases which have required adequate operative drainage of the stomach for relief of obstruction at the pylorus or in the duodenum.

Diarrhea: The second important complication following vagotomy is diarrhea. Frequently in the first few weeks following operation the patient will note a disturbance in bowel habits with several loose watery stools per day. This is usually a passing phase to be supplanted by a return to the usual normal behavior or to one to three softer stools per day. Occasionally, however, this frequency of watery stools may continue for weeks or even months. Such an established diarrhea may in some instances be associated with gastric stasis and be relieved by overcoming this factor. However, gastric stasis is apparently not the invariable causative factor. In fact, why removal of the vagus influence on intestinal movements should cause an acceleration of them is not entirely understood. Fortunately again, this complication is usually only a passing annoyance when it does occur rather than a serious problem as in the few instances recorded in the literature.

Failures: In all of the series, persistence or recurrence of ulcer symptoms or even proven ulceration has been reported. The investigators in the three clinics where the results of vagotomy have been carefully studied for the longest period of time are in agreement that the incidence of such failure of the ulcer to heal or of recurrence is low. Thus Dragstedt found in the first 160 cases in the University of Chicago series that 142 (89%) showed secretory evidence of a complete vagotomy, without a single instance of recurrent ulcer symptoms. In the 18 cases (11%) where physiological evidence indicated an incomplete denervation of vagus fibers to the stomach, five have had ulcer-mimetic pains since operation. Of the whole group then in this series, the incidence of presumptive recurrence or persistence of the ulcer is 3%, with another 8% presumably incompletely denervated but without symptoms to date. Moore has found recurrence of an ulcer or ulcer symptoms in five of the earliest 74 cases or 7% in the Massachusetts General Hospital series. Grimson had only two failures to suppress the ulcer symptoms in the Duke University series of 77 cases or 3%, while seven or 9% had a secondary gastro-enterostomy to relieve gastric stasis.

In two instances (Dragstedt) the persistence of the ulcer was definitely associated with intact vagus filaments found at a second operation. After division of the remaining nerve fibers the stomach no longer showed secretory evidence of vagus innervation and the ulcer symptoms and niches disappeared. In fact the relief of such persistent or recurrent ulcers by removing intact fibers is one of the most convincing evidences of the effectiveness of vagus denervation when complete. Whether all failures of permanent healing after vagotomy are due to such intact fibers is not yet proven.

A contrast to this favorable opinion appears to be expressed in other reports chiefly by Walters. He states that the results of vagus section are "inconstant, variable, and in most cases unpredictable." He also feels that the relief of pain may not be associated with the healing of the ulcer, citing in support of this possibility an unsuspected rupture of the ulcer after operation that occurred in the Mayo Clinic series and also the report of Weeks and VanHoy. In regard to this latter point the evidence is convincing. The relief of pain does not signify that the ulcer has healed. The time factor alone proves this fact. The healing of the ulcer after vagotomy takes many days or some weeks. (See section on Perforation and Subperforation). However, enough data has now accumulated, including X-ray examinations and evidence from secondary operation for gastric stasis with inspection of the ulcer site, to be quite sure that the great majority of ulcers heal after vagotomy. If the ulcer persists or recurs, the patient usually has typical ulcer pain. In a few instances we know an ulcer has recurred after vagotomy without such pain, just as there are silent duodenal ulcers that perforate or bleed without premonitory symptoms. We can feel reasonably sure, however, that the low recurrence rate reported in the series of Dragstedt, Moore and Grimson is a relatively accurate indication of the number of recurrent or persistent ulcers actually present to that date in their patients. The inconstancy in the results of vagotomy probably is due much more to (1) the irregular way in which post operative gastric stasis and constriction at the ulcer site express themselves, and to (2) the incompleteness of the denervation rather than to (1) the actual recurrence of ulceration after complete division of all vagus secretory fibers to the stomach or to (2) the regeneration of such fibers.

It would appear that physical healing of a duodenal ulcer following a complete division of the vagus fibers to the stomach is regularly or usually achieved. However, this does not assure the relief of basic emotional conflicts and their expression in other symptoms at least equally distressing to the patient. This type of "failure" following vagotomy has been shown by Szasz in a study of 16 post operative cases (for further discussion, see section on Psychological Evaluation).

PSYCHOLOGICAL EVALUATION

One of the most important causes of failures of any type of operation for duodenal ulcer has been the improper selection of cases. We have found an evaluation of psychic factors is as necessary as an analysis of physical data. In part I the hypothesis of the psychic origin of peptic ulcer was reviewed. Currently, clinical psychiatric investigations have led psychiatrists to stress the significance of emotional factors in the genesis and the development of gastro-duodenal ulcer. In fact, some investigators consider every peptic ulcer as being of psychogenic derivation with the background frequently in early infancy. We, as surgeons, recognize these factors in many of our ulcer patients, yet we feel that certain ulcers could be the result of abnormal chemical, vascular or humoral factors not directly related to abnormal psychic patterns. Also it is unknown why apparently similar psychic forces produce an ulcer in one individual and fail to do so in another. In some instances there appears to be a very direct relationship between life stress and the development of an ulcer. This is illustrated by the predilection for peptic ulcer in certain occupational groups; even doctors. As far as we are aware, no adequate study has been made to determine how many individuals, free of ulcer, have on investigation the same type of emotional conflicts and psychic disturbances thought to be of significance in the group with peptic ulcer. We anticipate further studies, jointly undertaken by psychiatrists, internists, physiologists and surgeons, to provide us with a more complete understanding of the role of these emotional factors in the etiology and course of peptic ulcer.

Despite the controversy regarding the basic causation of peptic ulcer there are several concepts we consider of practical value: (1) Presumably all cephalic stimulation of gastric secretion is mediated by the vagus nerve. Whether or not further study will indicate the primacy of emotional factors in the origin of gastro-duodenal ulcers, it is evident they modify considerably the clinical course. (2) In most of the ulcer patients *when seen by surgeons,* the psychologic patterns are of long duration and have become so fixed in the personality structure that psychiatric correction seems often unattainable. Psychiatric therapy with interviews and psychoanalysis is a prolonged procedure. Unless on superficial examination in such patients there is some evidence suggesting a favorable response, psychiatrists hesitate to undertake their treatment. (3) Even in the presence of an obvious psychiatric syndrome, operation may be necessary to save the patient's life from a complication of peptic ulcer. (4) Certain clinicians are doubtful of the ultimate total effectiveness of the ulcer patient after surgical treatment for the ulcer. Surgeons are certain from their experience that the majority of the patients submitted to operation have their effectiveness increased by relief of their ulcer symptoms. If this is not true in an individual surgeon's practice he is not properly selecting his patients. In elective surgery we attempt to exclude the patients in whom the ulcer is a mere incident in a profound psychiatric complex. We are currently engaged together with representatives of the Departments of Medicine and Psychiatry, in a study of our patients in this hospital. It is anticipated that further detailed study of the psychological aspect of this problem will be reported later by our group.

In fact estimation of the patients psychic pattern has been valuable to us in deciding for or against surgery and in selecting the type of operation. The classification proposed by Romano and his associates has been followed, viz: (1) *The classic ulcer type.* The patients are hard driving, outwardly independent, successful individuals where the outward activity is an overcompensation for deeply repressed desires. (2) *The dependent ulcer type.* This group seems superficially opposite to the first group. The patients are outwardly meek, shy and effeminate with dependent longings that are partially conscious. (3) *The psychopathic ulcer type.* This group reveals a character disorder. The patients are usually morally unreliable. Their dependent needs are expressed in child-like manners.

In group (3) the principle problem is that of the psychopathic personality and the treatment of the ulcer is secondary in consideration except for its complications of hemorrhage, perforation or obstruction. These people will not follow instructions, will not co-operate with the physician, they do rather poorly under any regimen. We do not operate on these people except as a last resort, and we feel that a new procedure like vagotomy should not be used under such circumstances. In group (2) there is considerable doubt concerning the wisdom of using vagotomy because the feeling of dependency may border closely on the psychopathic. In general, these patients get along fairly well following surgery and will follow instructions well. In group (1) vagotomy may be used without the above reservations when surgery seems indicated. Often patients in this group transfer their energies to the successful management of their disease, follow instructions well and are quite intelligent about their problems when carefully explained to them. In fact, vagotomy may be useful earlier than a surgeon would be willing to sacrifice a large part of the stomach. Indeed, in this group the benefit of interrupting efferent vagal outflow seems clearer than in the other groups. In this type of individual it may be feasible ultimately to employ vagotomy in earlier stages of the disease.

DISCUSSION

Sufficient time has now elapsed to judge the immediate and intermediate results of vagotomy in the treatment of duodenal ulcers. If the denervation is complete the great majority of patients will have an immediate and long lasting relief of their symptoms with the healing of the ulcer itself. The possibility has not been excluded that there may be certain instances where the acid-pepsin activity is increased above the tolerance of the duodenal mucosa from the chemical phase of digestion. Nor has the possibility been excluded that the mechanism of production in

certain duodenal ulcers is not related to acid-pepsin activity but exclusively to other factors (vascular, toxic, etc.). If such cases exist, Dragstedt's statistics would indicate that their number must be comparatively small.

The more serious question concerning the effectiveness of vagus denervation is whether its result will prove permanent. It is believed that the decrease in acid-pepsin is the effective mechanism which allows the healing of the duodenal ulcer. We know that in the course of time there usually is a marked decrease in the motor effects on the stomach which occur regularly after vagus denervation though to varying degrees. Also the longest older experiment on animals would appear to indicate a similar return of acid secretion after several months. These facts stress the issue whether eventually there will be such a return of excessive acid secretion and of duodenal ulceration in the vagotomized patient. Only the test of time will finally settle this point. However, we have reason to hope that the result of complete denervation will be permanent. There is already evidence that effective reduction in acid secretion has persisted up to four years. This question of ultimate recurrence cannot, therefore, be settled at present and will probably still be a live one for at least another decade.

In this connection, however, it is pertinent to call attention to two points. In the first place both anatomical studies and clinical experience prove the marked variability of the vagus components in the lower thoracic region (both in regard to the numbers of fibers as well as to their distribution). It has already been shown that recurrence can occur when any intact vagus fibers remain. In two instances Dragstedt has re-operated upon patients with recurrent or persistent duodenal ulcers accompanied by evidence of uninterrupted acid secretion. After the removal of an intact fiber left at the first operation, both of these patients had a typical drop in acid secretion accompanied by disappearance of ulcer symptoms. It is then of the utmost importance for the surgeon to assure himself that interruption of the vagal innervation to the stomach is complete. In our estimation this means for the trans-abdominal approach that the lower esophagus must be thoroughly mobilized so that the vagus trunks can be divided at a high point (8-10 cm. above the hiatus) and the lower esophageal plexus can be carefully removed fiber by fiber. In a number of instances the vagus nerve 10 cm. above the hiatus is not present as a single trunk on each side but is plexiform even at this level, or independent branches to the abdomen have come off of the right or left vagus higher than this point. We believe that those surgeons who pick up the vagus trunks below the hiatus and merely take out an inch or so of each will have many recurrences from the incompleteness of the operation. Such recurrences from incomplete removal must be carefully segregated in determining whether complete denervation is permanent in its effect.

In the second place, recurrence of ulcer must be carefully distinguished from the symptoms of pyloric or duodenal obstruction. After an interval free from symptoms if the vagotomized patient has reappearance of pain, this may be and frequently is due to such obstruction. In all of the large series, such cases are found. Such patients will be relieved by a proper drainage operation. In our own experience with transthoracic vagotomy without the institution of coincident surgical drainage subsequent pyloric obstruction has occurred with such frequency that we regularly make it a rule to combine effective gastric drainage (either Finney pyloroplasty or posterior gastro-enterostomy) with vagotomy. This also reduces the incidence of troublesome symptoms from gastric stasis which may persist for several weeks or even months after vagotomy alone. We acknowledge the validity of the point stressed by Lahey that when vagotomy is combined with gastro-enterostomy or Finney pyloroplasty the procedure viewed as an experiment becomes complicated. We know from the years of debate that either one of these procedures alone may alleviate symptoms. However, by the same token, we also know that the treatment of active duodenal ulcer by gastro-enterostomy or Finney pyloroplasty alone will be followed by a high incidence of anastomotic ulcers during the course of a 15 year period. There are now present a sufficient number of cases where only vagotomy was done to assess, over the period of the years, the result of this procedure in human patients as an uncomplicated experiment. It therefore, seems inadvisable to refrain from improving those results by a drainage operation merely because the improvement cannot then be ascribed alone to either vagotomy or drainage. The incidence of recurrence (particularly of bleeding) will ultimately show whether the relief usually seen following vagotomy is permanent or merely temporary.

Originally any degree of pyloric obstruction was considered to be a contra-indication for vagotomy. However, by combining with it adequate surgical drainage of the stomach it becomes a very satisfactory manner of dealing with the duodenal ulcer which has led to pyloric or duodenal obstruction, particularly in the older group. Every experienced gastric surgeon is very familiar with the problem presented. Frequently the patient has had ulcer symptoms over many years. At first his ulcer was quite amenable to treatment, but later it became more and more resistant. Exacerbations became more frequent and much harder to overcome by the usual conservative regime. There might or might not have been obvious symptoms of partial obstruction, but such an ulcer finally becomes intractable to medical management. On exploration the surgeon finds a marked deformity of the cap with an ulcer usually on the posterior wall surrounded by a dense zone of induration. Frequently the ulcer and its associated scar tissue almost encircles the duodenum. The situation of the ulcer on the pancreas and with the indurated zone extending close to the common duct and portal vein makes it a hazardous task in dissection. and as the base of the ulcer may extend into the substance of the pancreas, there is a definite danger of flaring up a serous pancreatitis by such dissection.

On the other hand, if this dilemma is met by resection above the pylorus then the antral mucosa should be entirely removed or it may increase the incidence of recurrent ulceration after subtotal gastrectomy. In our experience with vagotomy this group has responded particularly favorably to a combination of trans-abdominal vagotomy with adequate Finney pyloroplasty or posterior gastro-enterostomy. Also the combination of such adequate surgical drainage with vagotomy has apparently considerably reduced the trouble not only from gastric stasis but also from diarrhea. Frequently after vagotomy the patients will have a tendency toward loose stools for a few days or weeks, but this almost always becomes insignificant or disappears within three to six weeks.

COMPLICATIONS OF DUODENAL ULCERS

Pyloric Stenosis: A partial stenosis was discussed above. It was originally considered a contra indication to operation, but in our opinion, may be considered an actual indication for vagotomy combined with adequate gastric drainage.

Pyloric obstruction in what *appears to be* an inactive duodenal ulcer is the only legitimate indication for simple gastro-enterostomy in a good surgical risk. However, it is very difficult indeed to be certain that the biological factors which initiated the original duodenal ulcer are no longer acting. We know that after the recovery of the gastric mucosa from the secondary effects of tremendous gastric distention and stasis its secretory activity may increase again. With the modern methods of handling pre-operative preparation of the patient, overcoming the gastric distention, adjusting the mineral balance, and supplying necessary protein: many of these patients can be made good operative risks for more extensive procedure than simple gastro-enterostomy. Consequently, under these conditions, they may become candidates for a combined transabdominal vagotomy and gastro-enterostomy. It seems only logical that if vagotomy is effective at all, then it should assist in preventing the development of an anastomotic ulcer following gastro-enterostomy. Also combining vagotomy with subtotal gastrectomy to prevent the occurrence of anastomotic ulceration (incidence probably about 5%) may be a logical procedure if the occurrence of undesirable sequelae, particularly diarrhea, following this combination is not troublesome.

Perforation and Sub-Perforation: For acute perforation no one has suggested adding vagotomy at the time of closing the perforation. Such a combination would be entirely illogical as it would add a real danger of infection reaching the mediastinum. Repeated perforation, however, is evidence of an unusually active ulcer and as such is an indication for radical operative intervention. Here vagotomy is an active competitor with subtotal gastrectomy in the choice of the operation. Consequently, repeated past perforations may be considered an indication for vagotomy by those who elect this procedure in the unusually active ulcers. However, the ulcerative process in a sub-perforation may not be controlled quickly enough by vagotomy. Such ulcers on the point of perforation have gone on to actual perforation after vagotomy. Probably sub-perforation should be considered as a contra indication to vagotomy.

Acute Hemorrhage: During the active stage of bleeding, surgery is usually contra indicated on account of the low mortality of any single hemorrhage from a duodenal ulcer. However, by the modern method of massive transfusion combined with other supportive measures operation is indicated in some of these cases that bleed persistently. In such instances vagotomy will not stop the bleeding immediately after operation as it does the pain. Serious hemorrhage may continue or recur shortly after vagotomy. Consequently, in the actively bleeding ulcer when surgical intervention is considered proper, vagotomy should not be chosen. Repeated past hemorrhages are again a sign of an unusually active ulcer or one anatomically unfortunately placed. Allen has well stressed the increasing likelihood of further bleeding with each gross hemorrhage. Although the mortality of any one hemorrhage is low, the added mortality of repeated episodes becomes significant. Repeated hemorrhage is again one of the indications for drastic surgical intervention, and just as in the case of repeated perforation, vagotomy is a competitor with subtotal gastrectomy as the operation of choice.

JEJUNAL ULCERS

There is no dissension from the opinion that vagotomy is the preferable method of treatment when a jejunal or anastomotic ulcer occurs following subtotal gastrectomy, and is frequently so when such an ulcer follows gastro-enterostomy. The only technical question involved in such instances is whether the anastomotic ulcer should be coincidentally resected and the anastomosis revised. If the ulcer produced or its subsequent healing would produce a partial stenosis, then in our opinion the anastomosis should also be advised. Otherwise we believe it preferable in these cases to do a transthoracic vagotomy as this gives a little greater assurance of complete denervation. Such anastomotic ulcers were among the first cases in which vagotomy was applied and still stand at the head of the list of indications for it by all surgeons who employ this method of treatment. If intact excluded antral mucosa is present in such a case, vagotomy alone may not suffice to heal the ulcer. Its removal must always be considered, a procedure that may suffice to heal the ulcer even without vagotomy.

GASTRIC ULCERS

Our discussion so far has pertained only to duodenal or gastrojejunal ulcers. All reports are in agreement that the treatment of chronic gastric ulcers should not be considered with that of duodenal ulcer because of the danger of malignancy in the former. Approximately 15% of the gastric ulcers without obvious evidence of malignancy will eventually prove to be malignant. For this reason and the excellent results attained from subtotal gastrectomy, radical

section is the operation of choice for gastric ulcer. It is impossible to over-emphasize this fact. However, Dragstedt has suggested two possible exceptions to this important rule: (1) when there is a coincident duodenal ulcer with the chronic gastric ulcer, (2) ulcers so high on the lesser curvature of the stomach that total gastrectomy would be necessary to afford any chance for cure if the ulcer proves to be malignant. He suggests that in these two classes of gastric ulcer vagotomy may be considered. In the first instance, namely in the gastric ulcer that occurs coincidentally with duodenal ulcer the incidence of malignancy drops to 1%. The advantage in the operative mortality of vagotomy as compared with subtotal gastrectomy would probably more than compensate for the 1% danger of malignancy in the gastric ulcer. In the second instance, namely in the gastric ulcer high on the lesser curvature he proposes a therapeutic trial of vagotomy as an alternative to immediate total gastrectomy. Total gastrectomy with its higher operative mortality is then carried out with a clear conscience on the part of the surgeon if healing of the gastric ulcer is not promptly initiated by the vagotomy (as it frequently will be if the ulcer is benign). These two exceptions to the rule seem logical. Whether they should be adopted will have to be determined by accumulated experience. Again, however, they must be considered as exceptions only. Vagotomy is not a competitor with subtotal gastrectomy in the treatment of the gastric ulcer whether or not it appears to be malignant.

SUMMARY OF PRESENT STATUS OF VAGOTOMY

Subtotal gastrectomy has been evolved over a period of years to a point where it is a very satisfactory treatment of the intractable duodenal ulcer. In addition to a low mortality rate, it achieves a high percentage of excellent results with a small incidence of complications. Consequently, vagotomy to be a successful competitor of adequate subtotal gastrectomy must improve on or at least equal these high standards.

The immediate and intermediate results of vagotomy are extremely encouraging. The late results cannot yet be stated definitively. It is already apparent that an incomplete vagus denervation of the stomach fails to achieve permanent relief from the ulcer. This should constitute a warning to all surgeons performing vagotomy. Resection of short segments of the vagi from the abdominal approach has been tried several times in the past with disappointing results. We feel the abdominal approach is usually desirable, but extensive removal of all vagus trunk fibers, together with the esophageal plexus, for a considerable distance above the diaphragm is necessary to guard against incomplete denervation. We wish to emphasize that complete vagotomy must be supra-diaphragmatic though the approach may be transabdominal. Under these circumstances vagotomy is not a simple procedure to be undertaken casually. It is not a panacea for the surgeon inexperienced in gastric surgery. We feel this warning is a timely one in view of the uncritical enthusiasm for vagotomy which has spread throughout the surgical world.

Vagotomy should be used for duodenal or jejunal ulcers, not gastric ulcers. If this fact is not appreciated many patients with malignant ulcers, thought to be benign, will lose their only good opportunity for successful gastrectomy. Two possible exceptions to this rule, suggested by Dragstedt, appear to have some merit. The first is coincidental chronic gastric and duodenal ulcer which has only about one percent likelihood of malignancy instead of 15 to 20 per cent in isolated gastric ulcers. The second is the indurated ulcer so high on the lesser curvature that total gastrectomy would be required for resection as a potential malignancy. In the first exception the statistical possibility of malignancy is so low it may be disregarded. In the second exception the mortality rate of total gastrectomy exceeds the salvage rate of malignancy from the group. Consequently here it is legitimate on statistical grounds to perform a vagotomy which will result in the prompt healing of many of the benign ulcers in the group. At the end of only six weeks, total gastrectomy is advisable in all cases that fail to heal. This plan eliminates the comparatively high operative risk of *total* gastrectomy in the majority of the benign ulcers, while at the same time it allows, without undue delay, radical surgery for the malignant ulcer.

PERSONAL OPINION CONCERNING VAGOTOMY

All of the surgeons on our staff are interested in the long time follow up of our own cases of vagotomy and those recorded in the literature. However, the selection of vagotomy as the operation of choice in the surgical treatment of the chronic duodenal ulcer varies with the individual surgeon. All agree that in gastro-jejunal ulcers it is the logical choice, with or without revision of the anastomosis. From our personal experience we have come to the conclusion that vagotomy when used should be simultaneously combined with adequate surgical drainage of the stomach in practically all cases. We recognize that a great many of the cases can be carried through their period of gastric stasis by long continued aspiration, eventually attaining a satisfactory result from vagotomy alone. Dragstedt has emphasized the importance in this regime of preventing any post operative dilatation of the stomach. However, it is our observation that a certain degree of constriction exists in most chronic duodenal ulcers when they come to operation. Three of our 25 cases of transthoracic vagotomy who had healed their ulcer required operation for pyloric obstruction within one year. To prevent the necessity for such secondary operations as well as to eliminate transient stasis and diarrhea (which are the two chief complications of vagotomy) we now combine a pyloroplasty or gastro-enterostomy with vagotomy. We personally usually prefer pyloroplasty to gastro-enterostomy as it is more physiological and it avoids the occasional unfortunate sequelae of gastro-enterostomy. We wish to stress the fact that the only form of pyloroplasty

we use is the long horseshoe type (Finney-Haberer). This operation can be carried out in the presence of extensive induration and fixation of the cap, providing the duodenum is mobilized adequately along its lateral border and the incision at the pylorus goes along the the inferior border, instead of through the anterior surface. Rarely is the induration about the ulcer such that adequate lateral mobilization of the duodenum is inadvisable. The other exception to the use of the Finney-Haberer pyloroplasty is actual penetration of the ulcer into the pancreas. Here we feel that no manipulation in the neighborhood of the ulcer is justifiable.

Before considering any patient as a possible candidate for vagotomy there should be a careful psychological screening to exclude those in whom the ulcer syndrome is only one expression of a severe character disorder or psychopathic personality, (see section on Psychological Evaluation). Most of these cases are not candidates for vagotomy — indeed not for any type of surgery. On occasion the physical characteristics and complications of the ulcer may necessitate operation though it is recognized that the patient's major personality problem may remain uninfluenced, may be substituted for, or actually made worse.

We definitely feel that the patient with chronic duodenal ulcer should show evidence of excessive acid-pepsin secretion to be considered a candidate for vagotomy. Such evidence may be presented in any of the following ways: (1) A high concentration of free acid in the night secretion, (2) A high volume of night secretion even at moderate levels of acid concentration. (3) Abnormal amounts of acid in response to the insulin test (and possibly to histamine). We agree with Dragstedt's contention that the total amount of acid secretion (total milli-equivalents) is much more significant than the level of acid in any one sample (units of free HCl or pH).

We personally adopt vagotomy rather than subtotal gastrectomy in such patients where, from the clinical course, operation is indicated and the ulcer gives evidence of particular activity; namely, repeated hemorrhage, or perforation, or unusual difficulty in controling ulcer pain under ideal circumstances, or posterior penetration on the pancreas, or persistent acute symptoms in young adults. These constitute the indications for choosing surgical treatment in chronic duodenal ulcer with the exception of two important groups: First, the cases who were originally fairly well controlled medically but who have gradually become more intractable to such treatment; secondly those patients who for economic or sociologic reasons cannot or will not follow an ambulatory medical regime.

A. In the first group a long history of ulcer symptoms is invariably present, characterized by alternating periods of exacerbation and remission. The symptoms ultimately become intractable and persistent. A large element of pyloric or duodenal obstruction is usually present even though not necessarily demonstrated as a gastric residue by roentgenography. This group with an element of obstruction was excluded originally from the indications for vagotomy. Because of the protracted clinical course many of these patients are in the older age groups. In our experience, unless complete obstruction has seriously disturbed the nutritional and mineral balance, the combination of Finney-Haberer pyloroplasty with vagotomy is particularly advantageous for this group. The lower over-all mortality for subtotal gastrectomy is not a true index of the risk for such older patients. We have found that they tolerate vagotomy and such pyloroplasty well and that the results are excellent. We would like to stress the fact that partial obstruction should not be considered a contra indication for vagotomy when it is combined with an adequate pyloroplasty or gastro-enterostomy. If the patient cannot be made a good operative risk because of complete obstruction, sound surgical judgment dictates the simplest procedure that will relieve the obstruction, namely, gastro-enterostomy. This may be adequate, and if not, transthoracic vagotomy can be done later under more favorable conditions. The original transabdominal operation for overcoming the obstruction makes any secondary laparotomy much more difficult. Thus we find transthoracic vagotomy preferable to either trans-abdominal vagotomy or subtotal gastrectomy as a secondary procedure under these circumstances.

B. In the second group, operation is indicated because the patient cannot follow an ideal medical regime. Either the nature of his work precludes it, or else he is unable or unwilling to follow instructions. When the indication is largely an economic one, the choice of operation falls into the pattern outlined above. Vagotomy or subtotal gastrectomy will be chosen by the individual surgeon largely on the basis of his own personal opinion. When, however, the indication is due to lack of co-operation either voluntary or involuntary, we would like to warn the enthusiast for vagotomy against its use without careful consideration, particularly of the psychological survey. Such patients may come seeking operation as the easy way out of their psychological difficulties. The surgeon may relieve the ulcer symptoms if they are due to an organic lesion, but to his dismay may find new and equally disturbing symptom complexes. In fact, for either subtotal gastrectomy or vagotomy, this group is lowest in the order of indication and the choice of either of these procedures will depend on the individual surgeon and his estimation of the psychiatric, sociologic, and economic factors involved.

CONTRA INDICATIONS

In discussing the relative indications when vagotomy may be chosen over subtotal gastrectomy, we have already touched on the contra indications but we feel it is important to group them together. Vagotomy should not be used under the following circumstances: (A) acute hemorrhage, (B) acute perforation and subperforation, (C) complete pyloric obstruction (with metabolic imbalance), (D) gastric ulcer, (E) the group three psychopathic patient.

(A) Vagotomy initiates a fairly rapid healing of the ulcer, but this process requires several days and does not parallel the dramatic immediate relief of pain noted by the patient frequently on recovery from anesthesia. Consequently vagotomy should not be used for control of acute hemorrhage. When operation is indicated for this complication, a direct attack on the ulcer is necessary.

(B) In acute perforation with chemical bacterial peritonitis the opening of the mediastinum for the complete supradiaphragmatic vagotomy is contra-indicated. The sub-perforation where the ulcer base is very thin and anteriorly situated is also probably a contra-indication to vagotomy as perforation may occur before healing commences.

(C) Complete pyloric obstruction with altered metabolism and depleted reserves contra-indicates any operation except the simplest form of surgical drainage, namely gastro-enterostomy. After recovery from the obstruction if gastric secretory values are found to be high transthoracic vagotomy may be carried out secondarily.

(D) Gastric ulcer is an absolute contra-indication for vagotomy because of the possibility of undiagnosed malignancy. The two possible exceptions to this otherwise iron clad rule have been listed above in the section on gastric ulcers.

(E) The psychopathic patient in whom the duodenal ulcer is a mere incident in his personality problem is a candidate for major surgery only when a complication of the lesion endangers his life. We believe under such circumstances that a new procedure such as vagotomy should be avoided during its period of evaluation.

In conclusion then, our attitude is one of critical interest in the results so far attained by vagotomy as a treatment of the intractable duodenal ulcer. If the late results bear out the promise of the immediate and intermediate ones, vagotomy will be a valuable method in our surgical armamentarium. It may ultimately supplant subtotal gastrectomy in selected groups. It may be applicable to border-line cases where medical management is difficult, and to the problem of the young patient with a severe ulcer diathesis. Also its earlier use may save the patient, whose ulcer is gradually becoming obstructive, some years of pain and progressive disability.

Finally, we predict that in the immediate future the reports on the effectiveness of vagotomy will be extremely contradictory and confusing. There will certainly be a percentage of failure to achieve secretory denervation of the stomach, even following a most careful transabdominal but supradiaphragmatic vagotomy. There will be many more failures when the dissection has not been carried sufficiently high above the diaphragm. Thirdly there may be failures because of abnormal acid-pepsin secretion not under the control of the vagus or because of local conditions decreasing the resistance of the mucous membrane. Ultimate analysis will determine whether the total failures following vagotomy exceeds those following subtotal gastrectomy, and whether the failures are inherent in vagotomy as a method or due to inadequate technique in the individual case.

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Volume 18
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A Comparative Study of the Inhibitory Action of Chemical Agents on Peptic Activity

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PEPTIC ULCER is attributed to an excess of hydrochloric acid and pepsin in gastric juice (1, 2, 3). Ulceration of the gastro-intestinal tract by physiological concentrations of hydrochloric acid has never been produced in the absence of pepsin (4). Shock and Fogelson (5) demonstrated the significance of the pepsin factor in histamine produced ulcers.

It would therefore follow that in the treatment of peptic ulcer any compound which inhibited the action of pepsin should exert a beneficial effect. Numerous studies have been made of inhibition of the action of pepsin through the use of physical and chemical means; the results obtained are presented in summary (Table I).

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TABLE I

Compound	Concentration	Amount of Inhibition	Reference
Amino-monocarbonic Acids	Equal to HCl	50%	(7)
Egg Albumin		None	(8)
Proteoses	5%	Absolute	(8)
Gelatin	10%	Stops Proteolysis	(8)
Carbohydrates, Fat		Nil	(8)
Alcohol	32%	No Digestion	(8)
Benzoic Acid	1%	Absolutely Inhibitive	(8)
Sodium Benzoate	1%	Absolutely Inhibitive	(8)
Boric Acid, Sodium Borate		Nil	(8)
Salicylic Acid	Small Amounts	Distinctly Inhibitory	(8)
Sodium Sulphite	1:100	Prevents Proteolysis	(8)
Potassium Nitrate	1:400	Inhibits Proteolysis	(8)
Creosote		Strongly Inhibits	(8)
Glucose, Levulose, Galactose, Sucrose, Maltose, and Lactose	Dilute	Stimulates Peptic Digestion	(9)
Glucose, Levulose, Galactose, Sucrose, Maltose, and Lactose	Concentrated	Inhibit	(9)
Paraformaldehyde, Phenol		Inhibit	(10)
Sodium Chloride, Neutral Salts	2.5%	Complete Inhibition	(11)
Bile Acids		Inhibit	(12)
Alkali	pH 6	Enzyme Destroyed	(13)
Filter Paper Pulp	10 gm. in contact with pepsin solution	Varied with paper and concentration of pepsin	(14)
Aliphatic Acids		Inhibition	(15)
Unsaturated Aliphatic Acids		More pronounced Inhibition	(15)
Animal Charcoal	pH 1 to 2	Best Adsorption	(16)
Salicylic Acid		Inhibited	(17)
Aspirin		Inhibited to Less Degree	(17)
$Ca_3(PO_4)_2$		Pepsin Readily Adsorbed	(18)
Bi-Quinine Compound	10% Bi	Retards Action of Pepsin	(19)
8 $BiI_3.2C_{20}H_{24}N_2O_2.HI$	.0134% Bi	Retards Action of Pepsin	(19)
$BiOH(NO_3)_2.5CS(NH_2)_2$	Low Concentration	Retards Action of Pepsin	(20)
Zinc Sulfate	High Concentration	Retards Action of Pepsin	(20)
Magnesium Sulfate		Removes Pepsin from sol'n.	(21)
Cotton		Form Insoluble Complex With Pepsin	(22)
Edestin, Melon Globulin	34-40 Mols I/Mol. Pepsin	99%	(23)
Iodine	High Concentration	Inactive	(24)
Phloroglucinol	High Concentration	Inhibits	(24)
Phenol	High Concentration	Inhibits More Than Phenol	(24)
o-Cresol, m-Cresol, p-Cresol			

TABLE I (Continued)

Compound	Concentration	Amount of Inhibition	Reference
Pyrocatechol	High Concentration	Inhibits at High Concentration	(24)
Hydroquinone	High Concentration	Inactive	(24)
Resorcinol, pyrogallic Acid	High Concentration	Inhibits at High Concentration	(24)
Guaicol	High Concentration	Inhibits More Than Phenol	(24)
Veratrole	High Concentration	Inhibits More Than Phenol	(24)
Zephiran (Cationic Detergent)	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Igepon AP	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Aerosol OT	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Intramine (Anionic Detergents)	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Doxad Nos. 11, 21 ,23 (Anionic Detergents)	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Arctic Syntex A	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Tergitol-7 (Anionic Detergents)		Decrease Peptic Activity Moderately	(25)
Actival (Anionic Detergents)		Decrease Peptic Activity Moderately	(25)
Duponal P. C. (Anionic Detergents)		Inhibit Peptic Activity Markedly	(25)
Nacconale (Anionic Detergents)		As Effective as Sodium Alykyl Sulfate	(25)
Sodium Decyl Sulfate		Most Effective of the Alkyl Sulfates in lowering Peptic Activity	(25)
Sodium Dodecyl Sulfate		Most Effective of the Alkyl Sulfates in lowering Peptic Activity	(25)
$CaCO_3$, $Al(OH)_3$		Inhibition	(26)
Sodium Lauryl Sulfate	100 mg.	No Inhibition	(26)
Sodium Lauryl Sulfate	200 mg.	Decrease in Activity. If pH Remained Unchanged No Inactivation Occurred	(26)
Na Alkyl Sulfate		Inhibits in Absence of Lipids	(27)
$CaCO_3$, $Al(OH)_3$, $Mg(OH)_2$		Caused Decreased Peptic Activity Simultaneously with a Rise in the pH of Gastric Contents	(28)
Na Lauryl SO_4		Caused Decreased Peptic Activity Simultaneously with a Rise in the pH of Gastric Contents	(28)
p-Chloro, o-Chloro, and p-Bromo Phenol	All Equal	Most Active Inhibitor	(29)
p-Nitro Phenol	All Equal	↓	(29)
p-Amino Phenol	All Equal		
Phenol	All Equal	Least Active	(29)
Inverted Palmitic Acid		Pepsin Adsorbed	(30)
Inverted Cetylamine		Pepsin Adsorbed	(30)
Ultraviolet Light		Deactivates Pepsin	(31)
$Al_2(OH)_6$, $AlPO_4$, and $AlCl_3$		Inactivate Pepsin	(32)
$Mg_2Si_3O_8$ $25H_2O$		No Inactivation	(32)
Cl, NaOCl, I	15-65 Milli-Equiv. per Liter of Hydrolyzable Medium	Inhibited Profoundly	(33)
Na Lauryl Sulfate		Completely Inhibited	(34)
$CaCO_3$, $Al(OH)_3$		Inhibited $Al(OH)_3$ is better than $CaCO_3$	(35)
Na Alkyl Sulfate		Markedly Inhibits Peptic Activity	(36)
Na Alkyl Sulfate		When administered in conjunction with a diet low in fat — peptic activity is decreased.	(37)

EXPERIMENTAL

In this study it was decided to determine the effect of substances of varying chemical nature on peptic activity independent of change of pH. A comparative study was made of the inhibitory action of these substances on the digestion of coagulated egg albumin in vitro with a hydrochloric acid solution of 1:3000 N. F. Pepsin. The measurements were made by the method of Mett (6). The substances tested either proved indifferent or tended to check digestion. Where the substance tested was insoluble in the hydrochloric acid solution of pepsin, the mixture was shaken mechanically for 30 minutes. In each case where a mixture resulted, the peptic activity was determined on the supernatant liquid as well as on the heterogeneous mixture. The pH was held constant by adjustment with hydrochloric acid to pH 1.5 to 1.6 in order to obviate any effect caused by change away from the optimum for digestion of the egg albumin by the test substance. An aliquot of the mixture or solution after adjustment of the pH to 1.5 was then used to determine the activity of the residual pepsin. The volume of test solution or mixture in contact with Mett tubes was five cc. The results obtained are listed in Table II.

TABLE II

Substance Tested	Concentration mg/5 cc.	Conc. 1:3000 N. F. Pepsin mg/5 cc.	% Inhibition (Heterogeneous Mixture)	% Inhibition (Supernatant Liquid)
1. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	15	1.5	89	99
2. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	13	1.5	61	75
3. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	10	1.5	50	79
4. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	5	1.5	41	50
5. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	2	1.5	30	30
6. Insoluble Polyamine Anion Exchange Resin B, Commercial Sample 200 Mesh	15	1.5	95	100
7. Insoluble Polyamine Anion Exchange Resin C, Commercial Sample 200 Mesh	15	1.5	100	100
8. Insoluble Polyamine Anion Exchange Resin D, Commercial Sample 200 Mesh	15	1.5	65	100
9. Cation Exchange Resin A, Hydrogen Activated Commercial Sample-200 Mesh	15	1.5	26	None
10. Cation Exchange Resin B, Hydrogen Activated Commercial Sample-200 Mesh	15	1.5	40	40
11. Cation Exchange Resin C, Hydrogen Activated Commercial Sample-200 Mesh	15	1.5	49	49
12. Cation Exchange Resin D, Sodium Activated Commercial Sample-60 Mesh	15	1.5	75	44
13. Synthetic Sodium Aluminum Silicate-200 Mesh	15	1.5	0	75
14. Activated Bauxite (Essentially Al_2O_3)	15	1.5	88	94
15. Fullers Earth (Essentially SiO_2)	15	1.5	99	99
16. Synthetic Magnesium Silicate	15	1.5	75	94
17. Activated Charcoal	15	1.5	100	100
18. Diatomaceous Earth	15	1.5	19	19
19. Bauxite	15	1.5	44	58
20. Magnesium Trisilicate	15	1.5	84	84
21. Filtrol Adsorbent	15	1.5	88	84
22. Yeast Protein Hydrolysate	32	3.0	—	86
23. Lactalbumin Hydrolysate	40	3.0	—	88
24. Methionine	16	3.0	—	56
25. Glycine	16	3.0	—	78
26. Sulfonated Product of Fatty Acids and Aliphatic Compounds (Anionic Detergent)	15	1.5	—	84
27. Decyl Benzene Sodium (Anionic Detergent)	15	1.5	—	75
28. Cetyl Dimethyl Benzyl Ammonium Chloride (Cationic Detergent)	15	1.5	—	19
29. Sodium Oleate (Anionic Detergent)	15	1.5	100	—
30. Bentonite	15	1.5	100	100
31. Bentonite	10	1.5	100	100
32. Bentonite	6	1.5	100	100
33. Bentonite	4	1.5	99	99
34. Bentonite	2	1.5	61	83
35. Sodium Alkyl Sulfate, Principally Lauryl	15	1.5	100	100
36. Sodium Alkyl Sulfate, Principally Lauryl	10	1.5	—	100
37. Sodium Alkyl Sulfate, Principally Lauryl	5	1.5	—	100
38. Sodium Alkyl Sulfate, Principally Lauryl	2	1.5	—	100
39. Sodium Alkyl Sulfate, Principally Lauryl	1	1.5	—	84
40. Sodium Alkyl Sulfate, Principally Lauryl	0.5	1.5	—	53
41. Graphite Powder	15	1.5	None	None
42. $Al(OH)_3$ Powder	15	1.5	89	92
43. Salicylic Acid	15	1.5	63	—
44. Nicotinyl Salicylic Acid	15	1.5	41	26
45. 1 (+) Histidine HCl	15	1.5	None	—
46. 1 (+) Tyrosine	15	1.5	None	None
47. 9-Aminoacridine HCl	15	1.5	None	—
48. Gentian Violet	15	1.5	81	—
49. Oil Black (Dye)	15	1.5	None	None
50. (Bentonite	5	1.5	72	72
(Insoluble Polyamine (Resin A	5			
51. Bentonite	7.5	1.5	93	93
(Insoluble Polyamine (Resin A	7.5			

TABLE II

Substance Tested	Concentration mg/5 cc.	Conc. 1:3000 N. F. Pepsin mg/5 cc.	% Inhibition (Heterogeneous Mixture)	% Inhibition (Supernatant Liquid)
52. Bentonite	5	1.5	88	100
(Insoluble Polyamine (Resin A	10			
53. (Bentonite	7.5	1.5	100	100
(Sodium Alkyl Sulfate	7.5			
54. (Bentonite	7.5	1.5	97	97
(Synthetic NaAl (Silicate	7.5			
55. (Insoluble Polyamine (Resin	14.5	1.5	94	100
(Sodium Alkyl Sulfate	0.5			
56. (Insoluble Polyamine (Resin	14	1.5	99	100
(Sodium Alkyl Sulfate	1			
57. (Insoluble Polyamine (Resin	13	1.5	100	100
(Sodium Alkyl Sulfate	2			
58. (Insoluble Polyamine (Resin	10	1.5	100	100
(Sodium Alkyl Sulfate	5			

CONCLUSION

The specific inhibitory power of an insoluble polyamine resin was enhanced by the addition of small amounts of sodium alkyl sulfate, principally lauryl; as low as one part of the sodium alkyl sulfate in thirty of the resin was effective. The mechanism of this combined reaction has not been fully evaluated, although it has been previously stated (34) that sodium lauryl sulfate acting independently has a protein denaturing action. Peptic activity has been inhibited by many diverse agents and various mechanisms of action have been advanced to explain this. Charcoal (16), alumina (38), $Ca_3(PO_4)_2$ (18), proteins (22), proteoses (8), etc., have been shown to adsorb pepsin; colloidal $Al(OH)_3$ to precipitate it with an excess of acid again liberating the enzyme (39), and others (13) have shown it to be destroyed by alkali at a pH 6.

The addition of the sodium alkyl sulfate to the polyamine resin not only increased the specific inhibitory power of the resin for pepsin, but also increased the speed of action with which this took place; the rate of speed with which acid was neutralized by the resin was increased and pepsin inactivation aided.

In the series of agents tested as pepsin inhibitors in this study, three or more mechanisms are operative. In the instance of activated charcoal, surface adsorption is the basis. In the case of protein hydrolysate, the mass action effect of end products is probably operative. With gentian violet, chemical interaction with complex formation is most logical hypothesis. Beyond question however, many other foundations of antipeptic activity exist and any one or combination of these may be responsible in a specific instance of enzymatic inhibition.

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NUTRITION

Vitamins and Hormones in Nutrition. V: Emotional Upset and Trauma

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THE PRESENT COMMUNICATION completes a series of five reports in which a number of etiologic entities in nutritional disturbances have been discussed. The first report (1) was devoted to the synergistic action of vitamins and hormones and the etiological factors involved in 200 cases of nutritional disorders. Detailed anaylsis of each factor was presented in the remaining publications in the series. Thus, the effect of hormone dyscrasia on vitamin absorption was described in the second paper (2). The third (3) demonstrated the role of infection in nutritional disturbances. The importance of food intake and the interference with food absorption as related to nutritional balance was discussed in the fourth paper (4). This, the fifth and concluding report in the series, will present in detail the significance of both emotional upset and trauma as etiological factors in nutritional disorders. In 50 cases or 25 per cent of the 200 cases emotional upset was either the primary or a contributing factor; and in only 15 cases or eight per cent did trauma enter the disturbed nutritional picture.

The importance of "emotional upsets" in numerous symptom-complexes is indicated in the voluminous literature which has appeared on this subject during the last ten years. Different terms are used to label these psychic disturbances such as anxiety state, neurosis, psychoneurosis, and psychosomatic disease. But the author prefers to call it "the emotional state." It has been asserted that no anatomical system or physiological function is immune from a psychosomatic upset, and in these patients, thoughts and emotions can conjure or initiate symptoms comparable to those encountered in disease. For example, complexes simulating cancer, with associated weight loss, weakness, anorexia, diarrhea, anemia, and actual pain, are not uncommon. There is no question that cell metabolism is altered in these emotional upsets. We have all seen marked physical changes occur in individuals who have had their peace of mind seriously disturbed, as for instance by financial reverses, a broken love affair, or the sudden death of a relative or close friend. In extreme cases prolonged emotional upset may cause loss of appetite, diminished food intake, and loss in weight. This results in improper vitamin absorption

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which in turn leads to hormone dyscrasia and finally nutritional imbalance. Recognition of this chain of facts is extremely important to the practitioner, as far too many patients have been called neurotic, and no studied attempt made to help them. The realization that the psychic state is ill defined and may be of short duration, but may lead to important physical changes which can be treated successfully, would not only benefit many of these so called neurotic patients, but would also be a definite step toward the ideal of preventative medicine.

The importance of the emotional state as an etiological factor in faulty nutrition can best be illustrated by the following three cases. Detailed physical examinations as presented in earlier reports will be avoided, and because of the similarity in the pattern of the physical findings in most of these cases, physical and laboratory data will be brief, with emphasis only on pertinent findings.

Case 1. The first case is that of a 33 year old, white, unmarried female stenographer, who complained of recurrent attacks of headache, nausea, vomiting, blurred vision, fatigue and irritability, of six months' duration. Similar attacks in milder form had started at age 10 and had increased in frequency for two years, when, with the onset of menstruation, they had subsided. For the next eight years the patient went along fairly comfortably, except for the annoyance of acne vulgaris on the face, chest, and back. At age 20 she had a so called nervous breakdown, for which she could provide no reason other than overwork. Careful questioning revealed that a love affair had been broken very abruptly at this time. Following this and for the next twelve years attacks recurred, but they were relatively mild and infrequent. During this interval the patient practiced masturbation, at times excessively. Six months prior to consultation the attacks became very severe, and occurred about every ten days. During attacks and at intervals between them the patient experienced frequent episodes of palpitation, choking sensation, and joint pain. She was tense and irritable, with frequent outbursts of temper, and at times was possessed by the fear of insanity. On several occasions she had contemplated suicide. Delving further into her sex history, the patient admitted having fallen in love about fifteen months before this first consultation. She further stated that she had normal sex relations with this lover who later forced her into practicing various forms of sex perversion. The onset of her present symptoms coincided with the time when she broke away from this man.

Further history revealed that menstrual periods were regular, with slight dysmenorrhea and some leucorrhea. Since age 20 she had displayed sensitivity to certain foods. At age 21 she had urticaria and angioneurotic edema, and five years ago she had skin rash which covered her face, neck and hips. Her skin and hair which had previously been oily became extremely dry. She was subject to frequent colds and rare sore throats. Because of a fear of dentists she had neglected the care of her teeth. Her weight had remained constant until the past three months, during which she had lost eight pounds.

Physical examination revealed a well developed and well nourished female weighing 144 pounds. The head and neck presented classical deficiency changes. There were many carious teeth and roots, and marked sponginess of the gums. The heart and lungs showed the usual findings. The breasts showed unusual thickening through Cooper's ducts bilaterally, with added cystic changes in the left breast. There was pronounced voluntary spasm of the abdominal wall. Pelvic examination revealed marked hypertrophy of the clitoris, and cervical erosions which bled on slight pressure. There was considerable slightly purulent mucous discharge. The skin was unusually dry, with acneform lesions and scars on the face, back and chest. Reflexes were hyperactive throughout, but not pathological.

Laboratory data were at low normal levels. Basal metabolic rate was plus nine per cent. Hemoglobin was 82 per cent. Vaginal smears were negative for gram negative diplococci and trichomonas vaginalis parasite. Skin tests gave positive reactions to certain foods. The blood Hinton test was negative.

A full diet was prescribed, with due regard for the food sensitivities and acne. A simple regime of oral medication was prescribed, including α-estradiol, an elixir of the whole vitamin B complex, and a tablet containing a combination of an atropine derivative, ergotamine tartrate, and a small amount of phenobarbitol.

Much time was devoted to this patient in an attempt to establish self assurance and dispel the thought of suicide. She was not cooperative, and was lax in her appointments. Her response to the oral medications as outlined was fairly good, and the periodic attacks became less frequent and intense, although they still persisted. One year after the start of therapy a benign cyst was removed from the left breast. This surgery was performed at her own insistence because of a cancer phobia.

At the end of the first twelve months of therapy the patient was still somewhat unstable emotionally, and the attacks continued to recur, although not as severe. Analysis of her history during the first twelve months of treatment revealed that these attacks occurred during the time of corpus luteal hormone production in the menstrual cycle. They appeared principally eight to twelve days after the beginning of the menstrual period, or four to two days before the onset of the period. She was therefore given a short course of parenteral substitution therapy, following the normal course in the cycle, with anterior pituitary like hormone, α-estradiol benzoate, corpus luteum hormone, and thiamine chloride. To her oral medications was added a capsule containing vitamins A, D, C, with minerals, and amphetamine sulphate five mg. on arising. Following this her condition improved considerably, and she was finally relatively free from attacks. At check-up examinations during the next eighteen months physical findings corresponded with this improvement, and laboratory data were at good normal levels.

For the next three years this patient served in the W. A. C. S. Upon her discharge she appeared for check-up examination. Emotional stress of her war work had resulted in return of all her previous symptoms, to a much more marked degree. Migrainous attacks were more intense and more frequent than ever before. Menstrual periods were somewhat irregular, late, with considerable dysmenorrhea. She showed a loss in weight of 22 pounds. While in service all her teeth had been extracted, and dentures fitted, which accounted for some of her weight loss, similar to that reported in other cases (4). The patient stated that she was in complete control of her sexual desires except for rare phases of masturbation.

Physical examination at this time showed her to be thin, well developed, but poorly nourished, high strung, and weighing 122 pounds. Head and neck showed the usual changes although not as pronounced, except for pallor of the mucous tissues. She wore complete dentures, and the gums were well healed. Only slight thickening remained in Cooper's ducts of the left breast. Heart and lungs were of the usual type except for a few inspiratory wheezes throughout both lungs. The liver was slightly enlarged. Pelvic examination revealed no changes from

the original examination. There was considerable improvement in the acneform lesions. Fingernails showed marked softening and ridging. Reflexes were normal.

Laboratory data were at low levels. Hemoglobin was 72 per cent, red blood cell count 3,590,000. Fasting blood sugar was 99 mg. per 100 cc. of blood. Basal metabolic rate was plus 17 per cent.

A full diet was again prescribed. Oral replacement therapy consisted of *a-estradiol*, the whole vitamin B complex, a new improved multi-vitamin capsule.* A course of parenteral substitution therapy was given, including anterior pituitary like hormone, a-estradiol benzoate, testosterone propionate, crude liver extract, corpus luteum hormone, the whole vitamin B complex with ascorbic acid.

Response to this therapy was good. There was general subsidence of symptoms, and within three weeks her bloods had been brought up to a low normal level, with improvement of many of the physical findings. For the past six months this patient has been able to carry on with oral medications alone. She has gained eight pounds in weight, has been relatively free from migrainous attacks, and has maintained good emotional stability.

DISCUSSION

In this first case we have an emotional conflict which started at puberty and which continued throughout her normal reproductive period of life. The precipitating factors which contributed to and aggravated the emotional stability came at ten year intervals: First at puberty; second, a decade of overwork, financial concern, and a broken love affair. The third decade was marked by a more fortunate love affair resulting in normal sexual relations and terminated and ruined by sexual perversion. Then came a period of war hysteria with its multiple stimulae, and an attempt to run away from it all by enlisting in the W. A. C. S., hard work, dissatisfaction, and disillusionment. Finally an even greater emotional conflict was brought on by a beginning menopausal syndrome. Throughout this history of repeated and increasing emotional crises, an endocrine dyscrasia, aggravated by an infection in the teeth, cervix and skin, served to interfere with vitamin synthesis and absorption, which resulted in a physiological imbalance displayed clinically by severe nutritional deficiency.

Case 2. The second case is that of a 33 year old, white divorced female hairdresser, who complained chiefly of fatigue, irritability, and severe dysmenorrhea of six months' duration. Her general health had been good until about twelve months before, when she began to notice extreme and unwarranted fatigue, irritability, crying spells, shortness of breath on moderate effort, coldness of the hands and feet, some palpitation, occasional flushes, dryness of the hair and skin, loss of appetite and loss of weight. Menstrual periods had always been normal, a twenty-eight day cycle, with three day flow, except for occasional nausea and syncope during the past eight years. Six months ago she began to have severe dysmenorrhea accompanied by painful engorged breasts one week before the onset of the period, as well as considerable palpitation and intermittent claudication just before. Severe migrainous headaches coming at varying times during the cycle had started about twelve months previous to consultation. Periods became very irregular and scantier, coming at fourteen to twenty-one day intervals. The patient's work was difficult, the hours long, and entailed her standing on her feet most of the day. The occupational hazard of toxemia from the hair dyes used in her work had been ruled out by toxicologic blood, urine and stool studies.

The patient had been married for seven years, and during the past five years had been subject to severe emotional and mental strain, due to her husband's excessive drinking. The marriage finally culminated in separation and divorce. A cautious but minutely detailed history drew from the patient an admission that throughout her marriage she had always had an absolute horror of sexual relations with her husband. She stated further that the act had been painful and that she had never experienced an orgasm. The patient professed unqualified frigidity.

Pysical examination revealed a thin, well developed but poorly nourished female weighing 96 pounds. The usual deficiency changes were present in the head and neck, involving the eyelids, buccal mucous membranes, and the tongue. There was thickening in the upper and outer quadrant of the left breast, involving Cooper's ducts. The heart and lungs were characteristic. The blood pressure was extremely low, 88 systolic, 54 diastolic. There was hyperesthesia of the abdominal wall. There was lymphadenopathy of the cervical, axillary and inguinal glands. Pelvic examination was done with great difficulty because of the patient's extreme hyperesthesia. The cervix showed a superficial erosion which bled on slight pressure, and there were numerous small cysts on the anterior lip. There was moderate mucous discharge. The skin was thick and dry, and there were numerous tiny pustules over the back, and an occasional one over the anterior chest. The nails were extremely soft and brittle. The extremities were cold and there was slight coarse tremor of the extended fingers.

Laboratory data were at low normal levels. Basal metabolic rate was plus seven per cent. Blood Hinton and Wassermann tests were negative.

A full diet was prescribed, and a regime of complete substitution therapy was outlined. Oral medications included thyroid extract, an elixir of the whole vitamin B complex, a-estradiol, vitamins A, D, C, with minerals. Parenteral therapy was given twice a week, including a-estradiol benzoate, thiamine chloride, corpus luteum hormone, anterior pituitary like factor, liver extract, pregnant mare serum, testosterone propionate, and the whole vitamin B complex.

Under this regime there was considerable improvement, with subsidence of many of the subjective complaints. After three months of therapy the menstrual periods became more regular, of longer duration, and free from dysmenorrhea. No breast pain or sensitivity was noted. The migrainous headaches had diminished markedly. The appetite improved, and she gained five pounds. Her mental attitude and outlook for the future seemed brighter, and her whole condition showed decided improvement.

Physical examination six months after the start of therapy showed marked improvement. The head and neck were essentially normal. Slight fullness remained through Cooper's ducts in the left breast. There was slight improvement in blood pressure, 95 systolic, 56 diastolic. The abdomen showed less hyperesthesia. Pelvic

* Material supplied through the courtesy of Rawl Chemists, New York 3, New York. Trade name "Rawl Vite." Each capsule contains: Vitamin A 10,000 U. S. (B_1) P. units; Vitamin D 500 U. S. P. units; Thiamine (B_1) 10 mg.; one mg.; Calcium pantothenate five mg.; Nicotinamide 50 mg.; Ascorbic acid (C) 100 mg.; Alpha-Tocopherol (E) 10 mg. The oily vitamins are separated from the water soluble vitamins by a special coating which prevents breakdown and absorption of the oily vitamins by the gastric juices, but permits them to go through to the duodenum and jejunum where they are absorbed.

examination was somewhat less difficult, with decrease in the hyperesthesia. The cervix was essentially normal. There was no discharge. There was almost complete disappearance of the pustules of the skin. Except for small inguinal glands the adenopathy was absent. Extremities were warmer, the nails firmer.

Laboratory data were at good normal levels. Basal metabolic rate was minus three per cent.

This patient has been maintained at good normal levels for five years. Final solution of her marital difficulties, followed fifteen months later by a second happier marriage, aided greatly in stabilizing her emotionally, there was definite stimulation of the libido, and the patient admitted having an orgasm. Parenteral therapy was reduced from twice per week as originally outlined to five times per month, and then four times per month. In the third year of therapy the whole liver capsules*, referred to in previous papers (3,4), were added to her mouth medications, following which improvement was accelerated, and she was able to go for periods of two and three months without parenteral therapy. Then booster courses were given.

It should be stated that during courses of parenteral therapy, given at weekly intervals, precision in time was essential for good results. This particular case was most unusual in this respect. For example, the patient was in the habit of receiving her injections each week on a Monday, unless that day occurred during the first two days of her menstrual period. The menstrual period would be normal as long as this pattern was followed. However, should the patient vary the day of her injection by two or three days, for any one of the injections, or omit one in the series, she would have dysmenorrhea and usually intermittent claudication at her next period. This experience was proven time and time again. Actually it served as an indication for adjustment in parenteral therapy, so that she would receive an added injection the week before the menarche. Usually only two or three months of this adjustment was necessary to regulate the periods. In many cases it is just as simple an adjustment as this that will rectify annoying symptoms which return for no apparent reason, but which will discourage the patient, and sometimes prompt her to give up therapy prematurely. Particularly is this true of those cases which require parenteral therapy for over two years or more.

DISCUSSION

In summation, this case showed rather severe endocrine dyscrasia starting abruptly at age 32. It was complicated by poor dietary intake, and multiple emotional upsets, intensified by financial difficulties, obnoxious sexual relations, and the support of a drunken husband. Her complaints and symptoms were relieved by vitamin and hormone therapy. Moreover, peace of mind was obtained by correction of the causes of her emotional instability, and the desired result of nutritional balance was attained and maintained. Since original preparation of this report the patient has missed two menstrual periods, and at the present time is in the tenth week of pregnancy, which offers conclusive proof that oral and parenteral substitution therapy were responsible for the correction of her sterility.

Case 3. The third case is that of a 32 year old, white married male insurance statistician, who complained of attacks of fever, abdominal distress, nausea, clay stools and vertigo since childhood. He had been a "blue baby" at birth. At age three he started to have recurrent attacks of bronchitis, at age six he had bronchial pneumonia, at age eight he developed hay fever and asthma, and at age 13 he had lobar pneumonia. At this time, because of a question of tuberculosis, he was placed on a rest regime at home. Three years later, at age 16 he was able to resume a more normal life. He had always had chronic constipation. During the year prior to consultation attacks had become more severe, appearing at three week intervals, and starting with constipation or diarrhea, gastric distress, abdominal pressure, nausea, clay stools, vertigo, headache, elevated temperature and chills. Repeated chest X-rays had revealed chronic scars but no evidence of activity. With the recent attacks he also developed typical migraine headaches, lasting five or six hours, and leaving him with a painful head for three or four days afterwards. He had a chronic cough, more severe in the morning and at night, and productive of grayish white mucus, but no blood. For the past eighteen months he had noticed dryness of the hair and skin, bleeding of the gums, chipping and splitting of the nails, excessive perspiration, some pruritus, dysuria and frequency, and extreme fatigue, irritability and nervousness. At age 20 he had gonorrhea, which had apparently cleared under treatment. There was a positive family history of tuberculosis, evidenced in the deaths of his brother, uncle, and grandfather from this disease. He stated that he was greatly worried about his mother who had hyperthyroidism and anemia, and whom he professed to support.

Physical examination revealed a well developed, poorly nourished, thin male, weighing 151 5/8 pounds, height 69 3/4 inches. The hair was dry and lusterless, with some achromotrichia. The scalp was dry and scaling. Eyelids were edematous, ocular pressure was slightly increased, conjunctivae were of fair color, sclerae were injected. There was some narrowing of the retinal vessels and yellow brown pigmentation along the larger vessels. There was slight haziness in the antra and frontal sinuses on transillumination. Lips and mucus membranes were moist, dull, with fine leukoplakia throughout. There was marked sponginess and recession of the gums. The tongue was coated and papillae were markedly atrophic. There was erythema and follicular hypertrophy of the pharynx. The thyroid was full, particularly on the right. Small cervical glands were palpated. The heart was enlarged, the sounds distant, of fair quality, rate 66. Blood pressure was 92 systolic, 52 diastolic. The chest showed slight increased anteroposterior diameter with unequal expansion, and slight limitation of excursion in the right upper chest. There was a rachitic depression of the manubrium sternum. Vesicular breathing was elicited throughout the left lung, with rare medium crepitant rales and inspiratory wheezes. In the right lung there was slight dullness after cough, bronchial to bronchovesicular breathing in the upper half, increased vocal fremitus and vesicular breathing at the base with a few expiratory wheezes. The abdomen was soft, rounded, the liver moderately enlarged, smooth and tender. Small inguinal glands were palpated.

* Material supplied through the courtesy of Rawl Chemists, New York 3, New York. Trade name "Rawl Whole Liver Vitamin B Complex Capsules." Each capsule contains 0.5 Gm. of dessicated whole liver (equivalent to 2.5 Gm. of fresh whole liver) and provides:

Vitamin B complex factors: Thiamine (B_1) 1.0 mg.; riboflavin (B_2) 2.0 mg.; niacinamide 5.0 mg.; choline chloride 12.0 mg.; pyridoxine hydrochloride (B) 0.2 mg.; calcium pantothenate 0.2 mg.; inositol 5.0 mg.; biotin 0.6 mcg.; folic acid 10.0 mcg.

Amino acids: Methionine 11.0 mg.; arginine 19.0 mg.; cystine 4.0 mg.; glutamic acid 37.5 mg.; histidine 5.5 mg.; isoleucine 18.5 mg.; leucine 27.5 mg.; lysine 16.5 mg.; phenylalanine 10.5 mg.; threonine 11.0 mg.; tryptophane 2.5 mg.; tyrosine 10.0 mg.; valine 17.0 mg. The whole liver substance used in this preparation contains all the lipoid and water soluble B complex factors as found in fresh whole liver.

The genitalia were somewhat underdeveloped. The prostate was markedly enlarged and boggy. There was slight crepitus in some of the joints, with typical chronic pulmonary osteoarthropathy. The skin was thickened and dry, scaly, with generalized ichthyosis. There were numerous pigmented nevi and ephelides on the body. Extremities were cold, the nails were thickened, furrowed and pitted. There was slight coarse tremor of the extended fingers. Reflexes were hyperactive, more marked in the lower extremities, but none were pathological. Vibratory sensation was normal.

Laboratory data were at low levels. Basal metabolic rate was minus 17 per cent. Blood Hinton was negative.

A full diet, high in calories and vitamins was prescribed. Oral medications included thyroid extract, diethylstilbestrol, vitamin E., para-aminobenzoic acid, ketocholanic acid, the whole vitamin B complex, and mineral oil. Parenteral substitution therapy consisted of the anterior pituitary like hormone, a-estradiol benzoate, corpus luteum hormone, testosterone propionate, desoxycorticosterone acetate, thiamine chloride, liver extract, and ergotamine tartrate. Prostatic massages were given once per week.

Improvement was seen in the general condition within a few weeks after the start of therapy. At this time, through his estranged wife, an entirely different social and psychic history was obtained, which was later reluctantly corroborated in part by the patient. His wife described his shiftlessness, financial instability, and frigidity, stated that his professed concern over his mother's health was untrue, and that he did not support her. It was further learned that the patient was under suspicion of embezzlement from an insurance company. From this additional information a clearer insight into the patient's history was gained, and his emotional status became a major etiological factor. His apparent bravado was nothing more than a defense mechanism, acting as a shield for an inferiority complex and fear of prosecution.

The patient continued on the regime of oral and parenteral substitution therapy as described. At check-up examination three months later his condition was definitely improved. He was not as fatigued nor irritable, had only one attack of constipation and gastric distress, only two mild migraine attacks, was coughing less, and generally felt much better. He had gained seven pounds in weight.

Physical examination showed general improvement. The hair and scalp were more moist. There was improvement in the condition of the eyelids and conjunctivae. Retinal vessels appeared to be more normal. Transillumination revealed clearing of the haziness of the sinuses. Lips and mucous membranes were moist, of good color. Leukoplakia were markedly diminished, and the gums were firmer. Lingual papillae were more pronounced, the tongue was not as heavily coated, and there was no tremor. There was less erythema of the throat. The thyroid was smaller, and only a few cervical glands could be palpated. The heart was essentially normal in size, the sounds of better quality, rate 60. The blood pressure was 98 systolic, 60 diastolic. Lungs showed greater expansion, broncho-vesicular breathing at the right upper lobe persisted. There were practically no rales, nor rhonchi at the bases. There were slight inspiratory wheezes anteriorly bilaterally before cough. The abdomen was essentially normal except for a barely palpable liver. The skin was more moist, with a marked decrease in scaling and improvement in the generalized ichthyosis. Genitalia were more developed. Extremities were warmer, the nails were firmer and less ridged, and there was no tremor. Reflexes were more normal.

Laboratory data were at good normal levels. Basal metabolic rate was plus six per cent. Prostatic smears were negative after four months. Gallbladder drainage with a 50 per cent solution of magnesium sulfate had been done on three occasions, the last, one week before, was microscopically and chemically essentially normal for the first time.

This patient has been maintained for four years at good levels, with only a rare recurrence of attacks or subjective symptoms. His emotional status was considerably improved with some financial help, restitution with the insurance company, and improved libido. Parenteral therapy was given over an eighteen month period, but since then he has been maintained on mouth medication alone.

DISCUSSION

This third case presents a male who from the age of three was subject to allergies and recurrent infections which continued through puberty and, as frequently noted in other cases, resulted in nutritional disturbances and endocrine dyscrasia. As a youth and young man the infections persisted, with chronic foci in the lungs, gastro-intestinal tract, liver, sinuses and prostate. These infections and gastro-intestinal disturbances accounted for alteration in his food intake, and continued interference with vitamin and hormone absorption. Then, with the superimposition of severe mental and emotional strain the psychosomatic balance was seriously impaired. Eradication of the infection, plus substitution therapy materially aided the patient's entire physical and physiological status, helped him to achieve a better emotional control, and to restore normal nutritional levels. It should be emphasized here that in order to restore nutritional levels which had been depleted over some twenty-nine years, parenteral therapy was required for the first eighteen months, but once re-established, good physiological balance was maintained for well over four years with oral medications alone.

The importance of detailed history is well illustrated in the preceding three cases of nutritional disturbances in which emotional upset played so important a role. Human beings of average intelligence must necessarily go through some emotional upsets in their daily lives, at home, at work, or at play, particularly during the present post-war period of world wide economic and political unrest. Such upsets and their causes should therefore constitute an integral part of any medical history because of their extreme importance etiologically. This is also true in reference to the sex history. Unfortunately this phase of the medical history has frequently been neglected, but its significance, amply illustrated in these three cases just discussed, will be found in many others as well. A great majority of emotional upsets can be traced to altered or abnormal sex history. This does not indicate a Freudian tendency, but the profound significance of such disturbances has been well brought out by Kinsey (5) and his associates. Possibly their future observations will provide an answer to the question, what is normal sex life? How appalling that in this age of science and medicine little attempt has so far been made to establish a standard of so-called normal sex life.

Included in this communication, as already mentioned, is the discussion of another etiological group, trauma,

the smallest of the series, comprising only eight per cent of the total 200 cases. Three typical cases will be presented and discussed in detail.

Every physician must have been impressed at some time with the general effects of trauma far beyond the site of injury in one or more of his cases. Who has not seen a fractured spine or loss of an arm or leg cause complete remolding of the patient's future life, with resultant alteration in physical activity and eating habits, change in personality, varied mental reactions and even phobias. If trauma can effect a change in external reactions then certainly it can change physiological reactions, which in turn would alter individual cell metabolism, and result in physiological imbalance. Endocrine dyscrasia and vitamin deficiency would follow, with nutritional imbalance the end result. Again in these cases, the emotional status is extremely important, leading as it so often does to malingering.

The following cases may demonstrate more clearly the role of trauma in nutritional disorders.

Case 1. The first case presents a 51 year old, white married male house painter, complaining of increasing pain through the shoulders, neck, back, arms and legs of six weeks' duration, and fatigue, for the past two years. Seventeen years before he had fallen, injuring the right hip, and had been fitted to a back brace. He believed this to have marked the onset of his arthritic symptoms. Since then, in an effort to relieve the pain in his back he had worn arch supports, and at times a sacro-iliac belt. Eight years later he had again fallen, this time five feet from a ladder, after which he began to have stiffness on the right side of the neck. For the next seven to eight years he had recurrent pain in the neck and arms, severe headaches, and increasing fatigue. Three years ago he fractured the right humerus, and a year later he fell on the ice and fractured the left elbow. From then on generalized joint pain became more severe, and he began to notice paresthesias in the fingers, stiffness and puffiness of the joints in the morning. Six weeks before consultation he had received a course of physiotherapy, but the pain seemed to be worse after this. Eighteen years ago he began to have gastric distress with gas, epigastric fullness, pyrosis, and nausea. A gastro-intestinal series had been done, and a diagnosis of duodenal ulcer made. An ulcer diet, and Sippy powders were prescribed. Since then he had been subject to intermittent attacks of abdominal pain and pyrosis. He had noticed considerable reduction in libido during the past six years. Recently he had begun to have palpitation, sweats, flushes, was extremely nervous and tense, and had some crying spells. He had noted some prostatic symptoms during the past three years. During the past six months he had gained six pounds in weight.

Physical examination revealed a well developed, moderately obese, extremely nervous male, whose weight was 173 3/8 pounds, height 66 1/4 inches. He presented typical deficiency changes in the oral mucous membranes and hair. There were lesions on the pinna of both ears, resembling tophi but not characteristic. There were premature cataracts bilaterally. Ophthalmoscopic examination revealed tortuosity, arteriovenous nicking and calibre changes of the retinal vessels. The nipples were light in pigmentation, and there was an accessory nipple on the right. There was limited anterior and lateral motion of the neck. The heart was slightly enlarged, the sounds were of good quality and regular. There was a grade one systolic murmur at the apex and the pulmonary area. Second aortic sound was greater than second pulmonic sound. Blood pressure at basal levels was 166 systolic, 106 diastolic on the left arm, and on the right arm 172 systolic, 128 diastolic. After coffee the blood pressure was 178 systolic, 128 diastolic, on the right arm. The abdomen was essentially negative except for a liver palpable one finger below the right costal margin, smooth and slightly tender. The prostate was markedly enlarged and boggy at rectal examination. There were small axillary and inguinal glands. The skin was somewhat dry and thickened. There was crepitus through the larger joints and particularly in the right knee, with Heberden's nodes and thickening through the joints of the fingers and toes. The spine revealed limited motion in the dorsal and lumbar region. There were questionable tophaceous changes in the joints. Toenails and fingernails were thickened and ridged. There was a coarse tremor of the extended fingers.

Laboratory data were at low levels. Basal metabolic rate was minus seven per cent. Blood uric acid was 4.8 mg. per 100 cc. of blood. No positive tests for lead poisoning could be found. Blood Hinton test was negative. X-ray examination of the neck and spine revealed lipping of the margins with spur formation from the bodies of the vertebrae.

A well balanced diet of low caloric content was prescribed. Oral substitution therapy consisted of thyroid extract, diethylstilbestrol, the whole vitamin B complex, vitamins A, C, D, and a special tablet containing small amounts of d-N-methylamphetamine hydrochloride (d-desoxyephedrine hydrochloride), ketocholanic acid, and thiamine chloride*. Parenteral therapy was given twice per week, consisting of the anterior pituitary like factor, α-estradiol benzoate, corpus luteum hormone, testosterone propionate, deproteinated insulin free pancreatic extract, thiamine chloride, liver extract, and the whole vitamin B complex with ascorbic acid. Prostatic massages were given once per week. After one month on this regime his general condition at check-up examination revealed considerable improvement, and it was therefore possible to modify the parenteral therapy to once in two weeks, and to omit prostatic massages. At this time a course of bee venom injections were given for the joint pain, the patient receiving a total of fifty-seven stings (6).

The patient continued on this modified regime for three months, at the end of which his general condition was greatly improved. He complained of very little joint pain, had been relatively free from headaches, palpitation and flushes. Improvement of the prostatic symptoms and libido was noted. He was more energetic and had noted almost complete loss of nervous tension. He lost 11 7/8 pounds during this period. Although this patient had been more or less faithful to his regime of oral medications he had been somewhat uncooperative in the parenteral therapy, and actually had received none for six weeks prior to his check-up examination.

Physical examination revealed general improvement. His weight was 161 1/2 pounds. Head and neck were essentially normal. The tophaceous lesions on the pinna were smaller. The heart showed considerable reduction in size, the sounds were of better quality, regular, and the murmurs were of less intensity. Blood pressure was 140 systolic, 96 dia-

* Material supplied through the courtesy of Endo Products, Inc., Richmond Hill, New York. Trade name "Ganone Tablets." In two strengths of sugar coated tablets:

Green:	No. 1.	"d-N-methylamphetamine hydrochloride (d-desoxyephedrine hydrochloride."	3 mg.
		Ketocholanic acids (Triketol)	130 mg.
		Thiamine hydrochloride	1 mg.
Orange:	No. 2.	"d-N-methylamphetamine hydrochloride (d-desoxyephedrine hydrochloride."	6 mg.
		Ketocholanic acids (Triketol)	130 mg.
		Thiamine hydrochloride	1 mg.

stolic. The liver was smaller, barely palpable. The prostate was smaller, less boggy. The joints were much more freely movable, with less crepitus. The neck and spine revealed less limitation in motion. The skin was moist and of better tone. Extremities were warmer, the nails were firmer and less ridged. There was no tremor of the extended fingers.

Laboratory data were at optimal levels. Basal metabolic rate was plus three per cent. Blood uric acid was 2.2 mg. per 100 cc. of blood.

This patient has been maintained for ten months on essentially oral medications, with occasional booster injections. No return of major symptoms occurred, other than slight backache.

DISCUSSION

The first case in this group presents a male with an apparent neurotic tendency who at age 34 had fallen, injuring the back and hip, which necessitated his wearing a brace. This injury was followed at ages 42, 48 and 49 by repeated trauma. Following each accident there was a period of enforced bed rest which had accentuated the hypertrophic changes of the vertebral column already present. Under the stress of repeated trauma, and with the anxiety state which accompanied it, food intake, already limited by an ulcer regime, was further impaired. This had a deleterious effect on the absorption of vitamins and hormones and their synergistic action. Finally the classical male climacteric syndrome developed, completing the picture of physiological imbalance. The entire syndrome thus established yielded to substitution therapy with vitamins and hormones. Prostatic symptoms cleared with massages. Some gouty changes present responded to a short course of bee venom injections, given in conjunction with parenteral replacement therapy. Although marked improvement was admitted, the lumbosacral back, right hip joint and cervical spine were still constantly guarded by muscle spasm. Fear of trauma with its hardships could not be forgotten completely. Again the constant triad, endocrine dyscrasia, avitaminosis, and infection, now burning in the flame of trauma, resulted in a nutritional imbalance.

Case 2. The second case is that of a male retired surgeon, 58 years old, who complained of pain in the stumps of both legs for the past ten to twelve years. He had suffered from Meniere's disease for several years. He had severe painful vasospasm of the lower extremities, coldness of the feet and pain in the ankles, which increased in severity, and proved intractable to therapy. Following an acute attack of cholecystitis his condition became much worse. X-ray therapy was given for relief of the pain in his legs and during one treatment he received a burn which necessitated amputation of the lower third of both legs. Because of lack of circulation in the extremities the lines of amputation incisions did not heal for six months. Thereafter pain in the legs became constant and severe, with frequent attacks of claudication, typically a Berger's syndrome. He had suffered from constipation and spastic colitis for thirty years, as well as spasticity of the bladder sphincter for the past four years. These spasms were extremely severe, and were analogous to the night crises of tabes dorsalis. In an effort to relieve the pain of these abdominal and leg spasms, morphine was given at fairly regular intervals, and he eventually became addicted to this drug. He had been subject to frequent severe headaches, extreme nervousness, apprehension, jitteryness. Symptoms became more pronounced as the drug addiction progressed, and sanatorium treatment was finally necessary to break him of his morphine habit. He was discharged from the sanatorium supposedly cured.

It should be stated that this patient had been able to readjust his entire life by moving his family to Florida, and applying his surgical skill to handicrafts, such as woodcraft, pottery making, and painting. He would spend hours through the day working on these hobbies, in an attempt to busy himself and forget his pain. But in spite of all this the attacks of pain became more frequent and intense. For the past ten years his irritability, nervousness and apprehension were further complicated by depressions, crying spells and sweats, and for the past five years he had noted prostatic symptoms. With increased pain he began to resort to narcotics again. The patient had become well adapted to artificial legs, which he was able to keep on for varying periods during the day. He was unable, however, to do much walking. The patient had tried many therapeutic regimes, but with poor results.

Physical examination revealed a well developed, fairly well nourished male, whose weight was 135 pounds with artificial legs. Positive findings revealed the following. On fundal examination there was some pigmentation, narrowing, arteriovenous nicking and calibre changes of the vessels. Inferior turbinates were markedly hypertrophied, and the nasal septum was perforated, postoperatively. Mucous membranes showed considerable leukoplakia. Upper dentures were worn. The gums were somewhat soft and spongy, with some areas of recession. The tongue showed atrophic changes of the papillae, and there was slight tremor. There was considerable rigidity of the neck. The chest was barrel shaped. Blood pressure was 116 systolic, 68 diastolic, bilaterally. The lungs were hyper-resonant to percussion, with numerous coarse to medium crepitant rales at the bases bilaterally. The liver edge was palpable two fingers below the right costal margin. Examination of the extremities revealed amputation of the legs at the junction of the middle and lower thirds. The leg stumps were cold and moist, and very pale. Pulsations of the popliteal vessels could hardly be palpated. The skin of the thighs was cold in the lower third, and above that point it was warmer and of better color. Mercury oscillated weakly at 116 mms. around the calf, 116-118 mms. in the thigh, with much stronger oscillations. The skin on the body was dry. There were hypertrophic changes in all the joints, with limitation of motion in the shoulder joints. The fingers were cold, with slight coarse tremor on extension. Knee jerks were somewhat diminished. Biceps and triceps were slightly hyperactive. There was loss of brush sensation over the lateral aspect of both arms. Vibratory sensation was normal except through the lateral portions of the arms.

Laboratory data were at low normal levels. Basal metabolic test was not done at this time. Blood Hinton was negative.

Oral medication at first consisted only of a special capsule containing some amphetamine sulphate and ammonium chloride, given to improve circulation in the extremities. After two months there was less pain, less frequent attacks of claudication, and better general circulation. With this improvement the patient's mental attitude was better, he was less nervous, and bowel activity was improved. Because of the general improvement in his condition he was better able to fight off his desire for narcotics and kept away from them remarkably well.

At the end of the first two months oral medications were increased to include an elixir of the whole vitamin B complex, a capsule containing vitamins A, D, C, and tablets of both thiamine chloride and nicotinic acid. He continued on this regime for about fifteen months and noted gradual improvement.

Check-up examination at this time revealed definite improvement. Weight was 132 1/8 pounds with artificial legs. Fundal vessels showed increased dilatation. There was less hypertrophy of the inferior turbinates. Leukoplakia of the oral mucosa were diminished. Gums were firmer, and papillae of the tongue were more pronounced. There was less limitation of motion in the neck. Blood pressure was 124 systolic, 86 diastolic at basal levels. There were fewer medium crepitant rales at both lung bases, with hyper-resonance throughout persisting. The liver edge was barely palpable. The skin was moist and of better tone. The joints were more freely movable. The extremities were warmer. The skin of the stumps was warm and dry. Pulsations of the popliteal vessels were stronger. Reflexes and vibratory sensation were more normal.

Laboratory data also showed considerable improvement, at high normal levels. Basal metabolic rate was minus 11 per cent. A few prostatic massages were done, smears were loaded with pus cells.

At this time thyroid extract, methyl testosterone, and ketocholanic acid were added to his oral medications, and he was given a short course of parenteral therapy, consisting of testosterone propionate, α-estradiol benzoate, liver extract, and thiamine chloride. A short series of bee venom injections were given in conjunction with the substitution therapy. Two months later a calcium combination and vitamin E were added to the oral medications.

For six years this patient has been maintained on the oral medications as listed, and on a skeleton regime of parenteral therapy, consisting chiefly of thiamine chloride and liver extract. He has shown a gradual gain in weight and has been relatively free from severe subjective symptoms. His mental attitude was much improved, he was less nervous and tense, and entirely free from depressions and crying spells. Flushes were extremely rare, there was considerable improvement in his bowel action, and complete clearing of prostatic symptoms, with greater output. The constant pain had been obliterated. The severe crises-like attacks of intermittent claudication were extremely rare, and he had gone for as long as four months entirely free from them. Meniere's syndrome was completely absent as long as the maintenance dose of ammonium chloride was taken. An increase in severity of some of his symptoms, particularly recurrence of intermittent claudication, irritability, nervousness and flushes, all served as an indication that more parenteral therapy was needed, and the patient would ask for a booster course. It can be stated that the entire mental attitude was changed, and his outlook on life became more cheerful. The productive output in his hobby increased considerably. Narcotics were no longer indicated, nor desired.

DISCUSSION

In this patient operative trauma had changed the career of a highly successful, busy and energetic surgeon, to a life of semi-invalidism. There is no question that an emotional factor, too, was superimposed on the pathological processes involving almost every system in the body. Not only did the trauma and emotional status produce a deficiency syndrome, but they were augmented by drug addiction. Androgen-estrogen depletion and prostatic infection were also evident, and increased the already present avitaminosis, thus culminating in the inevitable nutritional imbalance. Although a pathological entity necessitated the amputations, one must attribute to the surgical trauma the initial etiological role in this complicated nutritional upset.

Case 3. The third case is that of a 51 year old, white, female, unmarried schoolteacher, complaining of nervousness, fatigue, and head pressure of ten years' duration. She stated that she had always been of "nervous temperament," but her general health had been good until fifteen years ago when she sustained a severe second degree burn caused by over exposure to the sun. After this she began to have recurrent attacks of chills, nausea, vertigo, and exhaustion, and noticed a marked loss of weight. An abscessed tooth was extracted at this time. Three years later she was told that she had colitis, for which she was given treatment. Symptoms were relieved but recurred within a short time. Two years later she was confined in a sanatorium for six weeks, with a so called nervous breakdown. The illness of her mother caused considerable emotional upset, after which she began to have frequent colds, pain through the neck and head, and increased nervousness. Seven years before consultation she was told that she had arthritis of the cervical spine, for which treatment was given, but only temporary relief was obtained. Five years ago she began to have constipation, pressure in the head, tremors, mental depression, and considerable joint pain, particularly in the elbows and knees, and very recently puffing of the fingers and toes. Menstrual periods had always been fairly regular, but were complicated by severe dysmenorrhea until relieved by medication twenty-two years previously. Periods had ceased three years ago, following which she began to have flushes, palpitation, increased fatigue. For the past seven years she was supposed to have had essential hypertension. A year ago she had been diagnosed "psychopathic" and shock therapy had been advised, but not received. She had noticed increased dryness of the hair and skin, brittleness of the nails, paresthesias of the hands and feet, and some intermittent claudication.

Physical examination revealed a well developed, fairly well nourished female, weighing 122 1/2 pounds. The usual findings of vitamin deficiencies of the head and neck were present. The heart was somewhat enlarged, the sounds of good quality and regular. There was accentuation of the first mitral sound, and the second aortic sound was greater than the second pulmonic. Blood pressure at basal levels was 158 systolic, 72 diastolic on the right arm; 188 systolic, 96 diastolic on the left arm; and 180 systolic, 88 diastolic after coffee. The lungs were negative except for bronchovesicular breathing at the right base with numerous coarse crepitant rales. The liver was palpable two fingers below the right costal margin, smooth, with slight tenderness on deep palpation over the gallbladder. There was slight tenderness over the descending colon. Incomplete pelvic examination revealed redness, glistening, and atrophic areas of the introital mucous membranes. At rectal examination uterus and ovaries were palpated, of senile type. There was crepitus in all the large joints, and beginning Heberden' nodes of the fingers and toes. There was generalized thickening and drying of the skin with superficial erythematous areas of pityriasis rosea, and a few tiny telangiectatic nevi. The hands and feet were cold, and there was considerable puffing of the lower extremities, but no true edema. Pulsations of the dorsalis pedis and posterior tibial vessels were extremely sluggish, particularly on the right. Toenails were thickened and firm, fingernails brittle and ridged. There was slight tremor of the extended fingers. Reflexes were markedly hyperactive, but none were pathological.

Laboratory data were at low normal and subnormal levels. Basal metabolic rate was plus 15 per cent. Blood Hinton was negative.

A full diet was prescribed. Oral medications consisted of the conjugated estrogens of pregnant mares urine expressed as sodium estrone sulfate, thyroid extract, an elixir of the whole vitamin B complex, a capsule con-

taining vitamins A, D, C, with minerals, ketocholanic acid, ammonium chloride, and a mild sedative. Parenteral therapy included the anterior pituitary like hormone, α-estradiol benzoate, testosterone propionate, deproteinated insulin free pancreatic extract, liver extract, thiamine chloride, pyridoxine hydrochloride, the whole vitamin B complex and ascorbic acid. Under this regime the patient responded quite well, showing good general improvement, and subsidence of many of her subjective complaints. About three or four weeks after the start of therapy the patient fell, and although she sustained only slight injuries she was considerably upset. Following this there was a return of many symptoms, in increased severity. Parenteral therapy was stepped up to twice per week, and dosage of some factors was increased. The whole liver capsule was added to her oral medications. Under this augmented regime her condition improved, and subjective symptoms once more subsided.

At check-up examination six months after the start of therapy her physical findings and laboratory data showed marked improvement. Appearance of the hair and oral mucous membranes was considerably improved. The heart was practically normal in size, the sounds were of better quality. Rate 60. Blood pressure was 152 systolic, 74 diastolic at basal levels. There was greater expansion of the lungs, vesicular breathing throughout, and no rales. The liver was barely palpable at the costal margin. There was no abdominal tenderness. Superficial pelvic examination revealed improvement of the vulval mucosa, with less redness and glistening, and fewer areas of atrophic changes. There was freer motion and less crepitus in the joints. The skin was moist and of good tone. Pityriasis rosea had disappeared. The extremities were warmer, dorsalis pedis and posterior tibial pulsations were more forceful. There was no puffing nor edema, and the nails were firmer and less ridged. There was no tremor of the extended fingers. Reflexes were quite normal.

Laboratory data showed considerable improvement at good normal levels. Basal metabolic rate was plus two per cent.

This patient has been maintained for the past eighteen months at good normal levels. She has omitted parenteral therapy for periods of two months at a time, with practically no return of symptoms. Her general condition has been much improved.

DISCUSSION

In this third case a second degree burn acted as the traumatic incident which aggravated a beginning ovarian dysfunction. Focal infection from a tooth further upset the endocrine imbalance. At the active menopause, at age 41, the patient had a complete nervous upset and was placed under sanatorium care. This was followed by arthritic complications, supposed essential hypertension at age 44, and at age 48 with the cessation of the menses and the usual vasomotor symptoms, such as flushes, headache, fatigue, mental depression, and crying spells. A diagnosis of "psychopathic" was finally made, and she was advised to undergo shock therapy. Here again we note the classic triad, endocrine dyscrasia, avitaminosis, and infection, but with the factors of trauma and emotional strain added, to bring about a pronounced nutritional imbalance. Oral and parenteral substitution therapy did much to alleviate most of this patient's complaints. The colitis, hypertension, nervous breakdown, were merely indications of a severe deficiency state. They were psychosomatic symptoms, the end result of the endocrine dyscrasia, avitaminosis, trauma, and malnutrition. They yielded readily to replacement therapy, and shock therapy was not necessary.

In these three cases, as in all cases, a detailed history is most important, particularly in establishing the time factor in relation to trauma, the onset of neurogenic symptoms and physical complaints. The tendency of the patient to refer back to a traumatic incident as the etiological factor in the common diseases occurring in the fourth and fifth decades of life, such as hypertension, arthritis, arteriosclerosis, and the like, can be misleading. The possibility of malingering should be considered carefully, and borne in mind at all times. Of prime importance, also is a detailed history of the eating habits just before and directly after trauma, as reduced food intake is a frequent sequel to trauma, and therefore a contributing factor to nutritional deficiencies (4).

Particularly significant in the three cases discussed is the fact that the major complaints developed at the climacteric period in life. It is at this age that we commonly observe personality changes, as well as changes in libido. Alterations in sex desire are most frequently observed during the reproductive years of the patient, and may present wide variations, ranging from impotence to hyper-activity, and in extreme cases even to perversion. These sex problems, of course, depend somewhat on the age of the patient at the time of trauma.

Perhaps the most important approach in this group, after infection has been cleared and complete substitution therapy has been given for the hormone and vitamin deficiencies, must be the consideration of the patient's mental status and his emotional readjustment after trauma. Religious faith, hobbies, or occupational therapy are especially useful to carry the patient over this transition period. The terrifying imprint of the traumatic incident just experienced remains still active in his mind, and often puts him in a constant state of fear. At such a time the physician must consider his patient as a whole, and not just a case of trauma. Mental relaxation through philosophical reassurance is most essential in the management of these patients. Attention only to the hormone dyscrasias, vitamin deficiencies and infection is not sufficient.

RESUME OF SERIES

Since preparation of the first paper in this series in the Fall of 1943, much has been contributed to our knowledge of nutrition. Inasmuch as the series covers a five year period, it would seem appropriate to review some of the discussions and predictions of earlier papers, and compare them with the advances made in this field. Research in nutritional problems has extended to all branches of science; not only to medicine, but also to surgery with its concern over the pre- and postoperative nutritional state, to dentistry, biochemistry, public health, agriculture, husbandry, — to mention only a few fields. Recent investigations

in biochemistry have revealed more about vitamins, added enzyme systems, provided better understanding of carbohydrate metabolism, shed some light on the little known facts in fat metabolism, and given us the first success in breaking down the protein molecule into individual amino acids as well as combinations found in hydrolyzed proteins.

For example, although the exact etiology of diabetes is still unknown, extensive research studies have conclusively proven that carbohydrates alone must not be considered, but all food elements, carbohydrates, fats and proteins must be studied together as each affects the others in the process of metabolism. Comparable to this is the fact that in the five groups chosen to be presented in this series, and analyzed in Chart I of the first paper, each was considered as a separate etiological factor in nutritional disturbances, but as has been frequently mentioned, several of them appeared and were interchangeable in a single case, and in many cases all five were present. Particularly was this evident in the sixth case under infection (3). In this case any one of several causes could have produced the prevailing nutritional and endocrine disorders. However, added together they resulted in greater deficiencies, and analysis of the history revealed that infection was the original and constant factor in every exacerbation. Throughout this series it has been stressed that the human body must be regarded as a unit, and treated as such. The variety of changes, histological, physiological, and biochemical, which can occur in the human body exemplifies the interrelation of all physiological responses, and is reflected either in physiological balance and good health, or pathological interference and ill health.

The discovery of antihormones and antivitamins has supplied further proof of the interrelationship and the protective action of hormones and vitamins towards each other. This synergistic action was demonstrated in the first paper, and has often been referred to in these studies. Even as early as 1934 in a clinical report on nine cases of achromotrichia, attention was called to the use of the whole vitamin B complex along with endocrine substitution therapy (7). Every publication since then, including the present series, has advocated complete substitution therapy with the necessary vitamins and hormones, parenterally and orally administered, as part of the therapeutic armamentarium. Furthermore, it has been constantly and specifically stated that hormones of most all the endocrine glands, as well as many of the known vitamins, are usually necessary to establish physiological balance. The 'triad" which has been mentioned so may times includes these two factors which must be replaced, and infection which must be eradicated.

The interrelationship between vitamins and hormones, as viewed by the endocrinologist, has been described by Professor Houssay (8) who writes, "There are between the endocrine glands reciprocal interactions which maintain them in a functional equilibrium (e. g. the hypophyseogonadal inter-relation) . . . Through all their mechanisms the glands of internal secretion contribute significantly towards the assurance of the units of the organism, the correlation of its parts, and the equilibrium of its function . . . Since the hormones regulate fundamental biochemical processes it is evident that every specialist in endocrinology must also be one of metabolism, and that conversely, every specialist in the diseases of nutrition must know endocrinology." In this description of the endocrine function in the organism it is noteworthy that consideration of the nutritional problem is included. The necessity for unimpaired synergistic action between hormones and vitamins in order to produce physiological balance and normal nutrition, has been repeated time and again in this series, and other publications as well. This is pertinently illustrated in the second case under "reduced dietary intake" (4), in which, although primary amenorrhea had existed throughout the lifetime of the patient, substitution therapy produced a normal menarche for a few months before establishment of the true climacteric. Particularly noteworthy was the fact that the nutritional status of this individual was at its best level during the short period when she had normal menstrual cycles than at any other time in her life.

Cancer research has been linked closer to the nutritional state of the organism as a whole than ever before. Recently cancer of the prostate and breast has been controlled by synthetic diethylstilbestrol and other synthetic chemicals possessing an estrone like action. The relationship of cancer to hormones has been considered in this series and in earlier publications (9). In many of the cases described in our reports diethylstilbestrol in small amounts has been used successfully, together with massages, for benign hypertrophied and chronic infected prostates. Its use in such cases was based on our own theory formulated when it was found that testosterone propionate was ineffective in the treatment for prostatic hypertrophy. Another reason for the use of diethylstilbestrol was our belief that it might act as a preventative agent against malignancy, but only after other glandular inactivity and vitamin imbalance were properly adjusted, infection had been cleared, and along with this the correct administration of the whole vitamin B complex. Time has proven that our use of the female hormone is most valuable in the treatment of carcinoma of the prostate. It is particularly useful in the alleviation of pain produced by the metastatic lesions, and yet without apparently affecting the size of the malignant tumor of the prostate gland.

The importance of the male climacteric syndrome as has always been stressed in these papers, has recently received further prominence by the work of Werner (10). Today the syndrome is far more widely accepted as a definite clinical entity which should be treated by substitution therapy. However, a word of warning should be issued against the continuous and promiscuous use of the androgen, testosterone propionate, alone. As indicated in the therapeutic principles discussed in this series, the male climacteric involves

an upset in both estrogen and androgen output, and therapy should consist in replacement of both of these factors in the proper proportion. This upset in the estrogen-androgen ratio, and the correct substitution proportions of both factors, has been mentioned repeatedly. In addition, in order to establish physiological balance the possibility of avitaminosis at this period of life must be considered, and substitution therapy administered for these vitamin deficiencies.

The growth of geriatrics into a full fledged medical specialty during the past few years has focused attention on another group which has hitherto been sadly neglected, namely the post climacteric stage in both the male and female. Many representative cases have been presented in this series illustrating the importance of the nutritional status in the aged, and its relation to many of the diseases of old age. Here again reference can be made to diabetes and its advanced therapy as an example of the importance of the nutritional picture. This new, broader approach in diabetes mellitus has been most effective in clearing up dermatitis, neuritic pain, and eye symptoms, and has been an important factor in reducing the incidence of amputations. So, too, maintenance of good nutritional levels in geriatrics has definitely aided in the improvement of the general circulatory system, gastro-intestinal and genito-urinary systems. The improved mental picture which usually follows alleviation of bladder and kidney symptoms has in turn resulted in improved vision, better gum and mouth hygiene, fewer decubitus lesions, improved bowel action, and improved bladder tone and control, often with the relief of incontinence. In some cases a decrease in the maintenance dosage of digitalis has been possible, and yet perfect compensation has been maintained. More recent knowledge of normal sex hormone productions makes it evident that even as late as the sixth and seventh decade in life the sex hormones, although no longer needed for reproduction, are still essential in maintaining the general nutritional picture. The sum and substance of this geriatric problem is adherence to the often repeated triad about hormone balance, vitamin balance, and freedom from infection, which opens the road to physiological balance and good nutritional status, and hence to better health.

Improved potency of individual hormones through conjugates and synthetics, and new factors in hormones like the purified growth hormone of Evans, have contributed much to enhance endocrine therapy. For example, the conjugate estrogens of pregnant mare's urine, which are water soluble and expressed as sodium estrone sulfate, are decidedly more potent orally than the estradiol and estriols are parenterally. This fact alone may change the entire status of oral estrogen therapy. Increased potency of implantation pellets of both male and female hormones, and vaginal suppositories of the female hormone, have recently been obtained, but there still remains much disagreement as to their efficacy. The topical use of hormones has been advanced by the incorporation of synthetic estrogens such as diethylstilbestrol or sodium estrone sulfate in a non greasy vanishing cream. The success of one such combination in the treatment of acne vulgaris has been mentioned in the present series (4). Similar creams have been extensively advertised by cosmetic houses, and recommended for prematurely wrinkled or dry skin. The topical use of these creams to promote breast or penile development has not proven successful thus far. Promiscuous use of these creams should be condemned, as many physicians, including the author, have observed metrorrhagia resulting from slow absorption of small daily doses of the synthetic estrogen.

Improved potencies and combinations of vitamins, and new vitamins or factors such as folic acid, and vitamin B_{12}, have provided more adequate means of combatting nutritional deficiencies. Attention was called in an earlier paper (2) to the ineffectiveness of iron therapy in many cases of anemia, and the prompt response of these same patients to complete vitamin and hormone substitution therapy. This observation is consistent with the present effective therapy of certain anemias with folic acid (11, 12), a factor of the vitamin B complex. A capsule containing whole liver and lipoids of liver with the essential amino acids was reported to be highly effective in the treatment of nutritional disorders. Possibly this new therapeutic agent, if administered along with folic acid, might provide a protective action against the latter's apparent deleterious effect on the spinal cord. The recent perfection of a water soluble vitamin A and D has done much to improve absorption of the vitamins through the intestinal tract. Unit comparison of the fat soluble vitamin A to the water soluble vitamin A is approximately 1:5. This increased potency has already proven of therapeutic advantage in certain intestinal diseases which cause interference in absorption of fatty acids, as for example, in atonic conditions of the bowel such as Hirschsprung's disease in children. There is fairly well established evidence that the water soluble fatty acids, particularly vitamin A, can be better stored by the liver, even in the presence of cirrhosis. This feature may prove extremely important in the nutritional picture in diseases involving the liver and general circulation. Para-aminobenzoic acid and its detoxifying action on certain drugs was mentioned in this series (3) and earlier reports (13, 14). Since then its action has proven therapeutically effective in combatting Rocky Mountain spotted fever (15), typhus fever (16), certain rickettsial diseases (17), and certain skin diseases (18).

Practical application of advances in the chemical breakdown of the protein molecule has produced hydrolyzed proteins, which have been commented upon in this series. Their use during World War II, along with another protein, blood plasma, was greatly responsible for the tremendous decrease in war casualties at the battle front. However, we must not lose sight of the fact that the proteins brought about essentially an improved nutritional status, which increased the casualty's stamina and enabled him to withstand further surgery or manipulation as needed.

In the post-war period the hydrolyzed proteins continue to be of tremendous value in intravenous therapy, and are also successful in oral therapy. In regard to oral administration, however, there still remains a provoking problem, of providing a vehicle that will make the animal hydrolyzed proteins more palatable, and hence more easily tolerated by the patient. When this is accomplished we should have an important therapeutic agent in restoring protein deficiencies and establishing a nitrogen balance.

This present review is in no way intended to be a complete coverage of the advances in nutrition over the past five years. Only certain therapeutic agents which have proven themselves as substantial aids in the solving of nutritional problems, and those advances in theory pertinent to discussions in the series have been mentioned. Medicine as a science is not, and should never become, stagnant. It is anticipated that by the time this report is published new hormones and new factors in vitamin therapy will have been announced. But, no matter how rapidly we may advance in the solution of details in nutritional problems, the structural pattern must include the correction of hormone dyscrasia, vitamin deficiency, and infection if complete physiological balance is to be established, and optimal nutritional levels achieved.

SUMMARY

1. In a series of 200 patients with nutritional disorders the significant etiological factors were classified into six groups, four of which were discussed in earlier reports. This, the final, is concerned with the remaining two, emotional upset and trauma, which occurred in 65 cases.

2. As in all reports in the series, six representative cases have been selected for discussion and analysis.

3. Emotional upset is of greater etiological significance than generally believed. Symptomatology which simulates specific diseases may result in physiological changes that lead to an impaired nutritional status.

4. Trauma may affect the emotional as well as the physical condition. This may lead to alteration in personality, physical activity, and eating habits, resulting in nutritional upset.

5. Careful history, including sex history, complete physical examination and laboratory tests, are all essential for proper diagnosis.

6. Correction of emotional instability, recovery from trauma or alleviation of its sequelae, eradication of any existing focus of infection, plus complete substitution therapy with vitamins and hormones, are essential to restore physiological balance.

7. Because this report is the final one in a series whose publication covers the past five years, a brief review of this period has been presented. This review includes advances in the chemistry of vitamins and hormones, their clinical application, and a discussion of their role in speeding up the restoration of physiological balance, so as to attain improved nutritional levels consistent with good health.

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Nutrition Notes

The Problems of Nutrition in India

Since Independence, the medical authorities and government in India are hastening to improve the chronically poor nutritional status of the country.

The Ministry has appointed a nutrition specialist, whose main functions are first, to advise the Central Government on all matters relating to nutrition, second, to assist in organizing nutrition work in centrally-administered areas and, third, to give technical advice and guidance to provinces in this field. Training classes for medical and non-medical men have been held at the Nutrition Research Laboratories at Coonoor. They have been carrying on basic researches in nutrition. Research grants have also been made to a number of universities, medical colleges and research institutes to investigate nutrition problems. The Ministry of Health instructed the India Supply Mission in Washington to pay the freight on 24 consecutive consignments of dry fat-free milk and multi-purpose food, offered as a gift from the U. S. A. through the good offices of the Watumull Foundation, Mrs. Pearl Buck and others. Some consignments have just arrived. Scientifically controlled growth experiments are planned to be carried out under the supervision of nutrition workers.

World Nutrition

The importance of *nutrition*, the world over, is summarized in the following excerpt from the Provisional Agenda of the first World Health Assembly, held at Geneva, Switzerland, June 24, 1948: "Nutrition is perhaps the most important single environmental factor influencing health. The discoveries of recent decades show that inadequate nutrition plays an important part in infant mortality, in the excessive proportion of under-developed school children and adolescents, and in the poor health and low productivity of a large number of adults. The availability of all kinds of foodstuffs has diminished, and there is a dire need for improvement in the nutritional sphere in most countries. It is considered desirable that WHO should be in a position to assist governments towards solving their nutritional problems and to stimulate the development and application of nutritional knowledge in the promotion of health. It is recommended that WHO establish jointly with FAO an expert advisory committee on nutrition consisting of not more than ten members, and a panel of corresponding members, and that suitable facilities be made available in the Secretariat to serve this committee, to supply information as required and to ensure implementation of the draft Agreement between WHO and FAO which was approved by the third Annual Conference of FAO and by the Interim Commission on 12 September 1947."

We have not, as yet, solved the nutritional problems facing us here at home in the U. S. A. There is a specific problem for each "class" in American society; poverty is occasionally the cause of malnutrition but iguorance almost always plays a part even among the well-to-do. There is a specific problem also for almost every geographic area in this nation which may vary from poor soil to transportation hurdles or local problems in agronomy such as water scarcity. Again, quantity of food-stuffs is less a threat than the quality of food-stuffs. It is necessary that all citizens of this country have enough to eat (sufficient calories) but it is becoming apparent that a more urgent need must also be served — namely, the supplying of non-devitalized articles of diet. We are suffering from the effects of a highly industrialized society (milling, storing, preserving, etc.) upon the character of our food. This is not evidenced by definite ill-health normally traceable to our "civilized complexity," but it is suggested by the remarkable claims of certain nutritionists who suspect that many illnesses may be traced indirectly to the absence of a perfect national diet. As yet we have never enjoyed perfect food products in the ultimate sense of the word. This, when it arrives, will constitute an ultra-refinement in selection, and in soil management. In the mean time, however, it is quite logical and certainly urgent that the ultimate food problem of all — starvation — should be met by this country in conjunction with other nations in world-areas where local governments are totally unable to cope, unassisted, with this saddest of all catastrophes.

The tragedy of starvation and semi-starvation is nothing new on the Globe, but the dislocations of war increased the incidence of food shortages and the war itself made us both food-conscious and world-conscious. There is some risk that, in joining this worthy crusade in nutrition, we may, to some degree, deplete our own stores of foods, but against this, quite apart from the moral issue, we may balance the increased knowledge of feeding which we shall acquire and the advantages of living in a world rendered better-humored by being better-fed. A vast majority of the citizens of the U. S. A. favor feeding starving peoples on principle — the simple principle of humanity — even if it should occasion hardship at home. On the other hand, there are indeed many citizens who would consider it sacrilegious to use food purely for strategic or political purposes. We are a peculiar people, with many admitted faults, one of which is our inability to admit that we are more generous than calculating. But the truth of our status in this respect has frequently been exemplified in fields other than nutritional. But here are starving people, so let's feed them.

The Liver in Anoxia and Malnutrition

The cells of the liver are so sensitive to lack of oxygen, and can be so profoundly affected in a short

time by anoxia from any cause, that it is now difficult to know how to kill an animal whose liver is to be examined histologically, because blows, poisons or bleeding all produce anoxia and give rise to histological changes of a remarkable character within the liver cells. It is probable that in the future biopsy methods will alone be considered to furnish reliable histological material from the liver.

The effect of anoxia is to produce in the liver two types of cellular modification (a) the vacuolated cell and (b) the so-called "plant-like" cell (1). These changes are not to be confused with fatty degeneration of the liver. Both vacuolated and plant-like cells are found very commonly in the liver (as well as glandular and muscular organs) after sudden death from suicidal hanging, judicial hanging, throttling, prussic acid poisoning, carbon monoxide poisoning, drowning, hemorrhage, and fractured skull. It is of interest that experimentally (2) the same types of cellular change were produced in the livers of dogs and rats by feeding low protein, high carbohydrate, low fat diets. In liver fragments removed by biopsy from adult pellagrins subsisting on a pure maize diet, the "plant-like" cells were found by Gillman and Gillman.

It would appear that the vacuolated and plant-like cells deserve greater attention since they represent one of the end results of malnutrition. The common factor in shock, poisoning, hemorrhage and malnutrition leading to the production of these abnormal cells obviously is anoxia of the liver, as part of a systemic anoxia. A high protein diet appears to reduce the probability of this abnormal cellular reaction occurring under the conditions which produce it. The abnormal cells appear to occur in cells having an abundance of chromidial substance and in cells, too, which are rich in glycogen. Beyond this fact, the pathogenesis of these abnormal cells is obscure. Gillman and Gillman seem to have produced a firm argument for the extreme susceptibility of the hepatic cell to lack of oxygen, and their work may well prove classical.

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Thiamin and the Heart

In monkeys, cardiac symptoms and lesions of the myocardium are produced only by diets that are *partially* deficient in thiamin, and permanence of the myocardial damage requires prolonged duration of the deficiency. In clinical medicine much remains to be learned with respect to beri-beri heart. As Alleman and Stollerman (1) point out, sometimes only two features may be present to suggest the diagnosis — (1) cardiac insufficiency unexplained by other etiological factors and (2) a history of a thiamin-deficient diet. Sometimes recovery is prompt and permanent following rest, thiamin and suitable management of the heart, even in cases of well-developed "wet beri-beri." At other times relapses occur and, where permanent myocardial damage is present, the prognosis for life is poor. So far as the heart condition is concerned the signs and symptoms show no important variation from those of heart failure due to other causes. However, when a good response to thiamin is obtained, a dramatic return of the enlarged heart to normal size occurs and there are only two other conditions in which this phenomenon usually is seen — arteriovenous aneurysm and myxedema.

Just how much of a role thiamin deficiency may play in American practice in cases of enlarged hearts is at present problematical, but many internists and cardiologists believe that thiamin should be used as a therapeutic test in instances where the etiological factor is not in evidence, where a dietary history suggests a thiamin deficiency and where there is an associated neuritis.

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Hospital and Food Conditions in Vienna

Following are some remarks by Chester M. Jones, M.D., Clinical Professor of Medicine, Harvard Medical School, with respect to his impression of the present day hospital and food conditions in Vienna as he found them during a recent sojurn there under the auspices of the Medical Mission to Austria by the Unitarian Service Committee in cooperation with World Health Organization:

The variety of drugs in a given ward is spotty. Penicillin is available in fair amounts. The most obvious lack is that of what we would consider basic dietary requirements. The caloric intake of all patients is limited, as in the civilian population. There is an added ration for hospital patients, and in addition one can obtain special supplements in certain urgent situations. This is more apparent than real. The total protein intake is at a low level. It is probably not more than 30 gm. a day, with rare exceptions, and it is less than this on five days a week. On two days there is a meat supplement. Under such conditions it is not possible to carry out good dietary therapy, and it is quite impossible to meet special caloric or protein requirements in an adequate fashion in post-operative states, or in conditions where tissue repair or healing is an important consideration. According to Colonel Cottrell and Professor Lauda, for the past two years the nutritional level of the average person has been just about marginal for maintenance. According to Lauda two phenomena have occurred. One is the clinical phenomena of marginal nutrition with a low red cell count and hemoglobin (3,800,000 and 65-707 -Sahli), together with slight underweight, slow pulse, and a diminution in physical pick-up, and a certain apathy. He has noted this in routine studies of his nurses. The serum protein is only slightly di-

minished, if at all, and there is no "hunger edema." This is quite different from the acute starvation that occurred during the first four to eight weeks of foreign (Russian) occupation when food was nearly absent, and emaciation and hunger appeared as a common phenomenon. The seeming effect of marginal nutrition that Lauda believes present is the lessened resistance to infection, and the increased complications resulting from it. Thus with ordinary pneumonia he thinks gangrene abscess formation is much more frequent. It is certain that gross malnutrition is not apparent.

Abstracts on Nutrition

OSCAR URTEAGA, B., ANIBAL ZAVALETA R., AND JORGE DIEQUEZ N.: *Observations on the pathology of intestinal parasitism.* (Arch. Peruanos d. Pat. y clin., June 1948, V. 11, No. 2, 215-246).

This is a preliminary report on disease in the city of Iquitos, Peru. Even normal controls all showed intestinal parasites, but patients with severe anemia showed greater infestation. Among the "normal" persons examined, much anemia was encountered — macrocytic, hypochromic with some megaloblastic marrow reactions. Nutritional factors were paramount in this group, and the anemia was regarded as tropical macrocytic anemia. Among the heavily infested patients, varying types of anemia were encountered. Chief interest of the authors is in conducting further studies on deficiency anemias in the Peruvian Selva.

JONES, C. M., CULVER, P. T., DRUMMEY, G. D., AND RYAN, A. E.: *Modification of fat absorption in the digestive tract by the use of an emulsifying agent.* (Ann. Int. Med., July 1948, V. 29, No. 1, 1-10).

Polyoxyethylene sorbitan monooleate manufactured by the Atlas Powder Co., Wilmington, Delaware, abbreviated "PSM" is a "wetting" agent which has an effect on the emulsification and surface tension and is used in industry to effect an even distribution of flavors, perfumes and lipoids in a watery or lipoid medium, was found non-toxic for animals and man and when fed by mouth greatly improves the speed and degree of fat absorption in conditions where fat waste is common, e. g. subtotal gastrectomy, sprue, pancreatic fibrosis, ileitis and in small bowel short-circuiting.

HEDGES, R. N.: *The influence of insulin on degenerative changes in diabetes mellitus.* (Illinois Med. Jour., April 1948, V. 93, No. 4, 206-210).

This is a study of hospital and other statistics concerning possible parallelism between peripheral vascular disease and the severity of diabetes. The conclusion is reached that although insulin may be used to control the glycemia in diabetes mellitus, its use does not check the development of degenerative lesions. There is also considerable lack of parallelism between the two aspects of the disease, since some mild cases of diabetes have marked vascular disease, and *vice versa*. There is no present therapy for the degenerative processes.

BLIXENKRONE-MOLLER, N.: *Shock and fluid problems.* (Nordisk Med., March 27, 1948, V. 37, No. 13, 615-620).

War shock is practically exclusively caused by loss of blood. In grading of shock, the blood pressure, pulse quality and the condition of the skin are of the greatest importance. During shock the blood is diluted by a fluid rich in proteins. There is full parallelism between the degree of shock, the amount of the blood lost and the blood dilution. The adequate treatment of shock is blood transfusion; plasma may be used as a temporary help. In peace-time surgery, the term shock is reserved for conditions caused by blood loss and accompanied by blood dilution.

"Shock kidney" is a clinically well defined picture (oliguria or anuria, acid urine with low specific gravity and albuminuria. The urine is red from excreted hemoglobin. Increasing azotemia. Perhaps slight hypertension). Microscopically there are seen deposits of hemoglobin or myoglobin in the kidneys. The treatment of this condition is reduced fluid supply (1,500 cc/24h) until the secretion of urine decreases.

The high concentration of potassium in the cells as compared to the extracellular spaces is emphasized. In dehydration, burns and shock, there is rapid loss of water and potassium from the cells; the excretion of potassium through the kidneys is increased. It may be advisable in such conditions to add potassium to the i. v. solution. If 0.9 per cent sodium chloride solution is given to a dehydrated patient the excretion of potassium is increased; physiological sodium chloride solution is damaging to the cells, dehydrates the cells and deprives them of potassium.

BROWN, A., CORKILL, A. B., FANTL, P. AND NELSON, J. F.: *Some observations on alloxan diabetes in the rabbit.* (Med. J. Australia, Feb. 14, 1948, 197-199).

From experiments on 25 rabbits which received diabetogenic doses of alloxan, the authors regard the initial hyperglycemia as due to a stimulation of the adrenal medulla and cysteine and glutothione probably produce a similar stimulation. In all their animals severe hypoglycemia resulted unless intravenous glucose was used. The destruction of the beta cells in the pancreas occurs quickly.

DAVIDSON, L. S. P. AND GIRDWOOD, R. H.: *Refractory iron-deficiency anemia treated with intravenous saccharated oxide of iron.* (Brit. Med. J., April 17, 1948, 733-734).

A patient responded dramatically to parenteral iron therapy subsquent to the failure of the oral administration of iron in large amounts for long periods, supplemented at various times with ascorbic acid, thyroid extract, molybdenized ferrous sulphate, parenteral liver extract and folic acid. However, in several other cases in which the saccharated oxide of iron was given intravenously, severe reactions have occurred. So it is suggested that further work is required on the preparation of solutions of iron for intravenous injection before parenteral iron treatment is used by general practitioners.

MORROW, A. W.: *Protein in health and disease.* (Med. J. Australia, March 6, 1948, V. 35, No. 10, 288-291).

There is no fixed protein reserve; it is a labile supply. Some ten of the 22 amino-acids are considered essential in the sense that the body cannot manufacture them in sufficient amounts to meet physiological requirements and they must therefore be supplied in the food. One gram of protein per kilogram of body weight is necessary for optimal nutrition in the normal adult. The "biological value" of protein depends upon its content of amino-acids, particularly those which are essential. Those races which exist on a reasonably high protein intake are more virile and energetic and less susceptible to infection than those whose intake is less.

Protein deficiency will lead to delayed wound healing. The importance of hypoalbuminemia with its consequent edema of the bowel wall and interference with gastro-intestinal function has not been sufficiently stressed. The best laboratory test is the measurement of the protein concentration in the blood serum or plasma. Parenteral therapy includes the administration of blood, plasma, albumin and various casein hydrolysates.

BROOKS, CHANDLER: *The control of body water balance.* (Med. J. Australia, Feb. 14, 1948, V. 35, No. 7, 187-192).

The associate professor of Physiology, Johns Hopkins Hospital, Baltimore, contributes the title subject to the Australian Post-graduate Federation of Medicine and presents as its main thesis the fact that a neuro-endocrine system of control is present which maintains a water balance essential to the existence of the organism. An enormously large literature has crystallized about this vital subject, much of which still defies solution. The essay is summed up in the statement of Hare: "It is probable that for the regulation of water exchange there is a system which includes the hypothalamico-hypophyseal mechanism which through its sensitivity to changes in the salt content of the blood controls the secretion of pituitrin and thereby the concentration in which salt is reabsorbed back into the blood." One striking fact is that men sweating profusely drink only half enough water to restore their loss and their efficiency and physical performance can be improved by "forcing" enough water to replace sweat losses. Thirst and kidney action are the two points at which control of water balance is maintained.

BROOKS, C.: *The role of appetite and hunger in control of nutritional balance.* (Med. J. Australia, March 6, 1948, V. 35, No. 10, 292-297).

A physiologist presents an extensive essay on the source of human energy, particularly the various classifications of food elements and dissertates upon the role of hunger and appetite in controlling energy intake. Energy output in its various forms is described. Diets with a high protein content tend to prevent hunger. Apparently there is a kind of specific appetite for what the body needs, e. g., sodium, calcium etc., and even the trace elements. Practically all dietary deficiencies result in anorexia.

KEETON, R. W., COLE, W. H., CALLOWAY, N., GLICKMAN, N., MITCHELL, H. M., DYNIEWICZ, J. AND HOWES, D.: *Convalescence: a study in the physiological recovery of nitrogen metabolism and liver function.* (Ann. Int. Med., March 1948, V. 25, No. 3, 521-548).

The negative nitrogen balance, and the fall in liver efficiency following surgical operations are best taken care of by a diet which contains twice the basal calories and excessive protein (2.6 gm. per kg.) administered by tube. Wastage of nitrogen due to infection is corrected by control of the infection. A positive nitrogen balance is augmented by ambulation in cases where the total calories given were only 120 per cent of the basal. Ambulation did not increase liver efficiency as measured by excretion of urobilinogen.

SCHIELE, B. C. AND BROZEK, J.: *"Experimental neurosis" resulting from semistarvation in man.* (Psychosom. Med., Jan.-Feb. 1948, V. X, No. 1, 31-50).

Thirty-six healthy young male conscientious-objectors volunteered for an experiment to determine the relative effectiveness of different types of diet in bringing about recovery from prolonged inanition. The mental reactions and personality changes were carefully observed by suitable techniques before, during and following the phase of semi-starvation which was sufficiently severe to cause them to lose, on the average, one-quarter of their body weight. It was found that a very definite neurosis was produced by the starvation, and it may be called an "experimental neurosis." The symptoms of the neurosis usually consisted of increased irritability, intense preoccupation with thoughts of food, depression, decrease in self-initiated activity, loss of sexual drive and social introversion. In a few cases the condition produced bordered on a psychosis. In all cases dietary rehabilitation cured the neurosis.

LEBAUER, S. F.: *Diabetes mellitus clinic: cardiovascular complications.* (South. Med. and Surg., Dec. 1947, V. CIX, No. 12, 393-394).

The author presents a man aged 45 who has been properly treated for diabetes for 15 years. Three years ago he developed a left hemiplegia. Now he shows tendencies to infection of the feet and shows also a bilateral hypesthesia from the knee to ankle. He also has intermittent claudication. The heart is enlarged and the EKG shows intraventricular block and evidence of coronary disease. The question arises as to the cause of vascular lesions in diabetes, particularly is diabetes a disease of fat, as well as carbohydrate metabolism?

RICHARDSON, F.: *Report of a case of diabetic gangrene treated with vitamin C and histidine.* (J. Arkansas Med. Soc., April 1948, V. XLIV, No. II, 238).

A woman of 63 with diabetes presented herself with advancing gangrene of the right great toe and obviously good results on the local circulation were obtained by "vitamin C and histidine injections every eight hours" day and night for 16 days, following the work of Wirtschafer and Widman who used this combination in endarteritis obliterans. No dosages are mentioned. It should be noted that the patient received suitable treatment with insulin, penicillin, as well as aminophyllin, and nicotinic acid.

Editorial

STRICTNESS OR FREEDOM IN DIABETES?

ARGUMENT STILL RAGES between the *purists* and the *free dieters* with respect to the treatment of diabetes mellitus. The purists insist that at all stages of the disease both in mild and severe cases, the blood sugar must be kept normal, the urine sugar-free, and polyuria avoided, as well as hypoglycemic reactions. As we all know, this becomes impossible in "brittle" cases, where hyperglycemia alternates with hypoglycemia under insulin treatment in spite of all due precautions. If an early diabetes is discovered requiring less than 40 units of insulin daily, it is probably important to apply the "purist" technique for, in so doing, the pancreas is put at rest and permitted to enjoy whatever reversibility it can command.

Where the disease is older and more than 40 units daily are required, it is at least arguable that no active acinar tissue remains in the pancreas. If this be true, then "purist" treatment cannot be expected to bring about any recovery in the pancreas, which may be considered dead with respect to insulin production.

The chief problem, in all but the earlier cases is, therefore, how much harm is occasioned to the body by a high blood sugar, by the urinary loss of sugar and by polyuria? At present there are no definite answers to these questions. Some authorities feel that an elevated blood sugar is beneficial in diabetes, and no one has proved that it is, or can be, responsible for the late complications of the disease — arteriosclerosis, nephrosclerosis, and retinitis.

On the other hand, there is evidence that a continuous hypoglycemia, such as may be encountered in active, metastatic benign pancreatic tumors, may exert a profound effect on the brain. In the early days of insulin it was a common occurrence to behold an arteriosclerotic diabetic kill himself rather quickly by strict dieting and overdosage with insulin, and, as a rule, death came via cardiac failure.

There is every reason to think that Tolstoi (1) should be considered right until he is proved wrong. At least he has offered a practical solution for the treatment of the severe, "brittle" diabetic; and free dieting, with a maximum of 50 units of Z. P. insulin daily, undoubtedly will do less harm than the frequent occurrence of insulin reactions of a severe grade. Mosenthal (2) shows that there is a "middle-of-the road" method which includes *some* dieting and *some* effort to maintain a lowered blood sugar and avoid polyuria with dehydration.

At present the individual physician is, of course, free to make his choice by methods. It will probably be several years before sufficient statistical evidence has been gathered to permit an accurate assessment of Tolstoi's ideas as well as those of the "purist" school. In the meantime, the effort at perfection in maintaining constant (?) blood sugar levels of a normal range involves the frequent sampling of blood and such strict adherence to a meticulous food intake, that life is rendered a great burden to the patient, who often rebels and goes berserk. Actually, the treatment of *any* diabetic, viewed in retrospect, is seen to be a record of hope and discouragement, of discipline and license, of resignation and rebellion, of success and failure and usually of final engulfment in that mysterious sea of degenerative processes which causes death. Tolstoi at least offers the individual a grateful degree of freedom as he pursues his course.

REFERENCES

1. Tolstoi, E., Almy, T. P. and Toscani, V.: Treatment of diabetes mellitus with protamine insulin: Is a persistent glycosuria harmful? A metabolic study of a severe case. Ann. Int. Med., 1942, XVI, 893.

2. Mosthenal, H. O.: Management of diabetes mellitus: an analysis of present-day methods of treatment. Ann. Int. Med. July 1948, V. 29, No. 1, 79-91.

Book Reviews

SYMPOSIUM ON NUTRITION. VOL. 1. NUTRITIONAL ANEMIA. Edited by Arthur Lejwa. The Robert Gould Research Foundation, Inc., Cincinnati, 1948.

This volume is composed of papers prepared for the symposium on nutritional anemia, organized by The Robert Gould Research Foundation, held in Cincinnati in October, 1947. Eleven specialists on various aspects of nutrition and anemia have presented comparatively brief and highly informative papers on such topics as folic acid, the metabolism of iron and copper, hypochromic anemia in infancy and the relationship of vitamin B-Complex and C to anemia. The introduction by E. V. McCollum reviews the history of anemia and mentions deficiency of cobalt as the cause of a microcytic hypochromic anemia sometimes fatal to cattle and sheep. The book is highly recommended to clinicians.

THE SURGERY OF THE COLON AND RECTUM. By Sir Hugh Devine and John Devine, Pp. 362, ($12.50). Williams and Wilkins, Baltimore, 1948.

This is an extremely able and condensed treatise on the title subject, very profusely illustrated, with many colored cuts. The authors have preserved a nice balance between diagnostic discussion and operative description. They have apparently written chiefly from personal experience and their acute observations suggest that they conform to the old English definition — "a surgeon is a physician who can operate." Physicians as well as surgeons should buy the book. The section on diagnosis of malignancy of the proximal colon is especially valuable.

CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT. By Maurice Feldman, M.D.,Pp. 901, ($8.00). Williams and Wilkins Co., Baltimore, 1948.

This is the third edition of a well-known and highly serviceable book which approaches the X-ray study of the digestive tract in a systematic manner. Practically all controversial matter has been omitted. The section on deficiency diseases is particularly attractive. Chief emphasis throughout is placed on the clinical aspects of disease. While this book is valuable to *any* physician, it is especially suitable for the internist or gastro-enterologist who does his own X-ray work, and is most highly recommended.

MEDICAL REARCH IN FRANCE DURING THE WAR, 1939-1945. Editions Medicales Flammarion.

Prof. Pasteur Vallery-Radot in association with Dr. Jean Hamburger of Paris, has gathered and presented 31 articles based upon research work done in France under the forbidding conditions of Nazi occupation. Referring to the research physicians, Professor Vallery-Radot, in his introduction, states — "They themselves led a miserable life, underfed, shivering with cold all winter, their minds beset with anguish. They lived under the constant threat of being deprived of their freedom, worrying about the fate of their family or of their friends who were thrown into jail, deported or shot. How could they be successful in their scientific work? And successful they were, in spite of all the torments of servitude, in spite of their physical and moral tortures, of almost overwhelming difficulties, of this wall shutting off France from the outside world, and in spite of this numbing silence about all countries not included in the German Reich. They succeeded in performing that herculean task: keeping the French mind alive. Their works are original and enrich the medical science with new contributions. This book will bear witness to this."

The Rockefeller Foundation enabled them to issue this book, obviously for the purpose of helping American physicians to realize how much excellent work was accomplished during the dark years — "years of German domination which aimed at blowing out every flame that was not a part of the Nazi fires."

A new disease, called the "neuro-edematous syndrome" was discovered, characterized by edema, diffuse pains, a peripheral type of paralysis, fever, tachycardia, obviously of epidemic type, sometimes progressing to recovery but, in other cases to death due to bulbar involvement. Rene Gutmann presents some careful work on early radiological diagnosis of gastric cancer. J. Caroli deals with radiometry of the biliary tract. Mallet-Guy describes "left chronic pancreatitis," a chronic sclerosis limited to the left portion of the organ, causing painful crises and ill-health, diagnosed on clinical signs and treated by "left pancreatectomy or left splanchnicectomy." Moulonguet decribes the successful treatment of endometrioma by testosterone. One of the painful privileges of the French physicians during the war was to study starvation states caused by malnutrition and Justin-Besancon analyzes bone changes under the title "Hunger osteosis." Besides the articles pertinent to gastro-enterology, there are many others of equal interest. Presumably copies of the book could be obtained from the Rockefeller Foundation.

General Abstracts Of Current Literature

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CLINICAL MEDICINE

STOMACH

FUREY, W. N.: *Roentgen observations in gastric ulcer.* (Mississippi Valley Med. J., May 1948, V. 70, No. 3, 98-102).

There are about 12 duodenal ulcers diagnosed for each gastric ulcer but the incidence of the latter is rising because of increased diagnostic acumen. Symptoms are of very little value in differentiation and reliance must be placed on X-ray examination, with gastroscopy in puzzling cases. The finding of a crater in the stomach is positive evidence of ulceration, but mucosal pattern disturbances, as well as spasm, are helpful. Where the gastric ulceration exceeds 2.5 cms. in diameter, is situated anywhere other than on the lesser curvature, or where it fails to respond promptly to medical treatment, malignancy should be suspected.

HOLST, J.: *Thoraco-abdominal and transthoracic resection of the stomach and esophagus for carcinoma.* (Nordisk Med., March 27, 1948, V. 37, No. 13, 620-624).

Of 12 total gastrectomies *per laparotomy*, four died in the postoperative period.

After 11 total *thoraco-abdominal* gastrectomies and four *thoraco-abdominal* resections of cardia and esophagus with esophago-gastrostomy, there was one postoperative death from coronary embolism.

The thoraco-abdominal incision gives better exposure, permits more exact suture and covering of the anastomosis and extensive removal of regional lymphatic glands in the ligaments of the stomach and the coeliac region.

Splenectomy had been performed in four of the operated cases. It is not expected that these new methods will be able to cure cases with carcinomatous infiltration of the major part of the stomach. Their advantage seems to be that they make the carcinomas of cardia, fundus and the left curvature technically operable, and that they permit more radical operation, including more radical extirpation of the regional lymphoglandular apparatus.

BOWEL

BROWN, C. H. AND COLVERT, J. R.: *Analysis of roentgen-ray diagnosis in carcinoma of the cecum and ascending colon.* (Ann. Int. Med., Dec. 1947, V. 27, No. 6, 936-943).

Roentgen-ray diagnosis of cancer of the cecum and ascending colon may be difficult. Carcinoma on the posterior side of the cecum is easy to miss. Obstruction occurs later in the ascending colon than in the rest of the organ because it is larger. But by careful study by means of enemas and spot films, repeated as indicated, the error in diagnosis can be kept down below 10 per cent.

VAL DEZ, F. C., GILBERT, C. S. AND KASH, W.: *Colonic diverticula: a review of 234 cases.* (Illinois Med. J., May 1948, V. 93, No. 5, 269-272).

The series of cases reviewed contains 122 cases of diverticulosis and 112 cases of diverticulitis. Diverticuli, unless inflamed, seldom produce symptoms, but when inflammation is present, pain of variable degrees of intensity may occur and the area in which pain is felt is not constant or characteristic. Bleeding may occur, otherwise anemia is uncommon. In the present series there were twelve obstructions, nine perforations, four carcinomas, four abscesses, one fistula and two massive hemorrhages. Conservative treatment includes rest, ice bag, smooth diet, saline enemas and atropine as well as sulfonamides. What is needed is better means of making a clinical diagnosis.

LAMSON, O. F.: *Acute appendicitis after middle life.* (Northwest Med., April 1948, V. 47, No. 4, 279-280).

The author reports on a series of 23 cases of acute appendicitis occurring in persons from 52 to 83 years of age with an average age of 63 years. He experiences a 25-3/5 per cent mortality and, on analysis of his data, finds that the high mortality rate is due to increased difficulty of making an early diagnosis in elderly persons. This is because, among the aged, the symptoms are not clear-cut and definite: severe pain may not occur in elderly persons until the appendix has already ruptured.

RITVO, MAX AND GOLDEN, J. LAURENCE: *The roentgen diagnosis of volvulus of the sigmoid with intestinal obstruction.* (Am. J. Roentgen. and Rad. Ther. 56, 4, 480. October 1946).

Volvulus of the sigmoid is an important cause of intestinal obstruction. It is a condition in which early diagnosis is essential as the mortality is high unless the condition is relieved promptly. The palliative measures applied in other forms of obstruction are ineffective in cases due to a volvulus.

Clinical diagnosis is usually impossible.

Barium enema studies offer a method of localizing the obstruction and demonstrating its cause. The characteristic roentgen findings in volvulus are linear, curved densities alternating with bands of increased radiance over an area several centimeters in length in the sigmoid colon. This corkscrew-like arrangement of the mucosal folds is pathognomonic of volvulus.

FRANZ J. LUST

FORTY, F.: *Associated carcinoma of colon and rectum.* (Proc. Roy. Soc. Med., Dec. 1947, V. XL, No. 14, 872-874).

Up until 1934, only 29 authentic cases of multiple primary tumors confined to the large bowel had been recorded. The majority of multiple primary tumors have affected unrelated systems or organs. Norbury (1931: Proc. R. Soc. Med., 24, 198) reported several cases affecting the colon and rectum and emphasized the importance of exhaustive examination of the entire colon for such a possibility before planning an operation aimed at removal of a single malignant growth. The author describes two such cases. The first case, a woman aged 61, showed primary cancer in the ascending colon near the ileocecal junction and another at the recto-sigmoid junction. The second case, a woman aged 38, had a cancer of the transverse colon and, four years later, a malignant papilloma of the rectum: in the interim she developed and had removed surgically bilateral secondary carcinoma of the ovaries. In both cases surgery was followed by good recovery.

MORGAN, C. N.: *Carcinoma of the cecum associated with carcinoid tumor of the small intestine.* (Proc. Roy. Soc. Med., Dec. 1947, V. XL, No. 14, 874-875).

The case is reported of a man, aged 65, from whom was removed a huge fungating adenocarcinoma from the cecum and a carcinoid tumor from the ileum. The association of a carcinoma and a carcinoid tumor is a very rare occurrence. Carcinoid tumors of the small intestine metastasize more frequently than those of the appendix.

RAVEN, R. W.: *Partial hepatectomy and right hemicolectomy for carcinoma of the hepatic flexure of the colon.* (Proc. Roy. Soc. Med., December 1947, V. XL, No. 14).

A man aged 38 had had an operation for carcinoma of the hepatic flexure of the colon invading extensively the right lobe of the liver, but was closed without any attempt to remove the tumor which was considered inoperable. He had developed a severe anemia. After blood transfusions, a large part of the right lobe of the liver including gallbladder and right half of the colon was removed. No evidence of secondary cancer, apart from the liver extension was found. The patient made an excellent recovery from the operation.

LLOYD-DAVIES, O. V.: *Carcinoma of the rectum with a single secondary in the liver: synchronous combined excision and left hepatectomy.* (Proc. Roy. Soc. Med., Dec. 1947, V. XL, No. 14, 875-876).

At operation, in addition to a large rectal cancer previously discovered, there was found a large single secondary in the left lobe of the liver. The left lobe was removed three weeks after the operation for removal of the rectal tumor. The patient made a good recovery but died two years later from a simple intestinal obstruction, because operation was delayed two days on the theory that the obstruction was due to secondary cancer. Actually, the obstruction was found to be due to a loop of small intestine becoming adherent to a Meckel's diverticulum. Postmortem examination showed no evidence of carcinoma.

MILLER, A. A. AND PECK, C. R.: *Balantidial dysentery (report of a fatal case in Assam)* (Brit. Med. Jour., March 6, 1948, 448-449).

Balantidial dysentery is very rare in India and indeed elsewhere. A man aged 30 was admitted to hospital with fever and diarrhea with blood and mucus, dying on the third day. All stool examinations had been negative. At autopsy ulceration was found in the cecum and ascending colon and a large ulcer from the pelvic colon showed the balantidium in histological sections well imbedded in the sub-epithelial layer. The pathological condition resembled that of amebic dysentery.

BOYD, J. T.: *Diverticulosis and diverticulitis.* (Texas State J. Med., March 1948, V. XLIII, No. 11, 681-684).

The author deals with diverticula of the colon, and emphasizes that an inflamed diverticulum may mimic almost any lesion of the large bowel. Diarrhea and constipation are equally common and bloody stools may be present. The disease may be suspected in every patient with abdominal symptoms who is over 40, whose symptoms have occurred over a period of time and whose pain is in the lower left or lower half of the abdomen. Carcinoma is differentiated from diverticulitis with extreme difficulty even at laparotomy.

PANCREAS

WAPSHAW, H.: *The blood diastase and lipase changes in acute pancreatitis.* (Brit. Med. J., July 10, 1948, 68-70).

The relative merits of two serum enzyme tests have been considered. The blood normally contains enzymes that are active on starch and vegetable oils. In ten cases of acute pancreatitis, the two tests were found equally satisfactory, though their clinical application seems limited to the initial stages of the disease. The serum diastase estimations may furnish information regarding the grade of severity of the disease.

LIVER AND GALL BLADDER

WOOD, I. J., KING, W. E., PARSONS, P. J., PERRY, J. W., FREEMAN, M. AND LIMBRICK, L.: *Non-suppurative hepatitis: a study of acute and chronic forms with special reference to biochemical and histological changes.* (Med. J. Australia, Feb. 28, 1948, V. 35, No. 9, 249-261).

In 32 cases of acute and chronic hepatitis the etiological factor in most cases was a virus. In one case nutritional deficiency influenced the course of the disease. Most of the 20 acute cases usually resolved in four to eight weeks and presented the classical signs — fever, abdominal discomfort, enlargement of liver, jaundice, dark urine, pale stools. In the 12 chronic cases the onset varied, some of them giving no history of an acute attack, probably because the initial attack was asymptomatic, and these cases drifted on for months and years with relapses and remissions. The cephalin flocculation test was the best single test for distinguishing hepatitis from obstructive jaundice. This fact applied also to chronic cases, where the albumin-globulin ratio also proved helpful. Aspiration-biopsy studies helped to diagnose hepatitis in cases where the jaundice was not clinically explainable.

WALTON, K. AND LEEDHAM-GREENE, J. C.: *Paracolon bacillus infection causing cholecystitis and suppurative hepatitis.* (Brit. Med. J., Dec. 27, 1947, 1033).

An officer of 36 had an acutely inflamed gall bladder removed, failed to improve and died 32 days later. Cultures of the pus from the gall bladder and of the patient's blood, as well as his liver at autopsy, revealed an organism which on careful study appeared to belong to the paracolon group, forming no gas on culture, and more specifically was related to Group B of Dudgeon and Pulvertaft's classification or to Group IV in that of Sevitt. The organisms of this group are difficult to classify. The liver at postmortem was badly infected.

RENNIE, J. B. AND RAE, S. L.: *Differential diagnosis of jaundice by flocculation tests.* (Brit. Med. J., Dec. 27, 1947, 1030-1032).

Cephalin-cholesterol flocculation and serum-colloidal-gold tests were done on 100 normal persons, 110 patients with hepatic disorders and 281 persons without clinical evidence of liver disease. The control cases all gave negative tests. Of 270 patients without evidence of liver disease the cephalin test was positive in 7.8 per cent and the gold test in 9.6 per cent — it may be that the presence of fever was at times responsible. In 32 cases of obstructive jaundice both tests were positive in 15.6 per cent. In contrast, 76.2 per cent of cephalin and 81 per cent of gold tests were positive in jaundice of hepatic origin, and complete precipitation was noted in more than half of the cases. The gold test appears to be the more satisfactory of the two tests since it is done with standard solutions of known chemical composition.

KJOLHEDE, K. T.: *Tuberculous cholecystitis.* (Nordisk Med., Feb. 7, 1948, V. 39, No. 27, 1292-1293).

Up till 1946, only 27 cases of tuberculous cholecystitis had been reported, in only ten of which a histological examination had been made. No typical clinical symptoms are met with. At operation, one finds a very thick-walled gall bladder, adherent to neighboring organs, and containing caseous purulent material. A case is reported in a woman of 53. There were no other signs of tuberculosis and the preoperative diagnosis was simply "cholecystitis." The diagnosis of tubercular gall bladder disease was confirmed by histological examination.

WELLMAN, G. O.: *Solitary pyogenic abscess of the liver: report of a case due to anerobic streptococci cured by penicillin.* (Illinois Med. J., June 1948, V. 93, No. 6, 327-330).

A case of solitary hepatic abscess due to anerobic streptococci is reported in which cure was effected solely by the use of penicillin. Three previous similar cases have been reported: one was found at autopsy ten weeks following surgical closure of a perforated peptic ulcer; one was cured by a two-stage transperitoneal drainage; and a third case was one of multiple pyogenic liver abscesses cured with penicillin after sulfonamides and surgical drainage had failed. Penicillin in massive doses offers a bright future for pyogenic liver abscess.

ULCER

STANDARD, S.: *The surgical management of peptic ulcers.* (Bull. U. S. Army Med. Dept., April 1948, V. III, No. 4, 310-315).

Peptic ulcer is primarily a medical disease, only about seven per cent eventually requiring surgery. Surgery is indicated in perforation, after one or two massive hemorrhages, in pyloric block, and where medical treatment fails after prolonged trial. Twenty per cent of perforations have no history of ulcer. Following operation for perforation, about 70 per cent have a recurrence within two years. The dictum that bleeding ulcers do not perforate and perforating ulcers do not bleed is generally true. The author, in the face of massive hemorrhage prefers to transfuse the patient and allow him to stop bleeding. If operation must be done, he prefers oxygen and cyclopropane with plenty of transfused blood. Of patients who have had two massive hemorrhages, 55 per cent fail to respond to medical care. A subtotal gastrectomy should be done especially in patients over 45 years of age. Subtotal gastrectomy ought to be done on cases of organic block of the pylorus. For those who do not respond to medical care, subtotal gastrectomy is indicated. Out of nine vagotomies, two have returned with atony of the stomach, pylorospasm and marked pain. The other seven cases have done well clinically but not always with X-ray evidence of healing of the ulcer.

The Experimental Production and Treatment of Peptic Ulcers

A Review of the Literature

By

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THE SYMPTOMS OF PEPTIC ULCERS appear to have been vaguely recognized by the ancients. Descriptions of the pathology appeared in the sixteenth century literature, while in the eighteenth century physiologists began to wonder why the stomach did not digest itself. It was not until the nineteenth century, however, that experimental studies on the pathogenesis of peptic ulcers were begun.

Perusal of the ancient Babylonian and Egyptian literature (213) fails to reveal any awareness of the existence of peptic ulcers. Hippocrates described the characteristic vomitus and stools, apparently without recognizing the cause, while Galen, Celsus and the other ancients in their descriptions of passia cardiaca, hematemesis and melena presented vague and uncertain references to ulcer as the causative factor.

With the revival of post mortem examinations in the sixteenth century, the earliest descriptions of ulcer of the stomach began to appear. One of the first clear descriptions was by Donati (45) in 1586. In the sixteenth and seventeenth centuries, the various anatomic features were described in excellent fashion by Donatus, Littre, Morgagni and Matthew Baillie.

Abercombie 1824) (1), Cruveilhier (39) and Rokitansky (174) not only gave accurate descriptions of the lesions, differentiating them from other gastric lesions, but also correlated them with the symptomatology and suggested a causative factor. Abercombie gave a detailed description of the symptoms, describing the pains or discomfort which may subside or be relieved by vomiting. Therapeutically he recommended milk, farinaceous foods, lime water and bismuth. Cruveilhier too recognized the importance of dietary regimen.

As to the primary cause, Cruveilhier suggested a preceding gastritis, anticipating a modern view. Another modern view, that hemorrhagic erosions were the basis for ulcerations, was expressed by Rokitansky (1841) (174). Armstrong (1825) (3) was one of the first to suggest the relation between nerves and gastric inflammation, while Rokitansky, in addition, suggested that ulcerative processes of the stomach and lower esophagus may have a neurogenic origin, being due to a morbid condition of the vagus. Virchow, in 1853, (220) laid stress on the corrosive action of the gastric secretion; however, he believed that in the defined ulcer the cause must be local i. e. due to vascular occlusion. Thus, the various theories preceding actual experimentation were outlined in the first half of the nineteenth century.

Experimentally, acute ulcerations have been produced by a great variety of procedures. Experimentors have been handicapped first by the fact that spontaneous chronic ulcers do not occur in any of the experimental animals employed; second, that chronic ulcers have only been produced with great difficulty, necessitating, as in the Mann-Williamson (137) technique, a marked derangement in the gastro-intestinal physiology; third, that the experimental techniques frequently have involved a number of factors, failure to recognize and evaluate which has led to a certain amount of confusion and difference of opinion.

Because of the wide variety of experimental animals employed, such as dogs, rabbits, cats, ferrets, woodchucks, monkeys, guinea pigs, rats, sheep, calves, chickens, ducks, pigs, etc., species differences have led to some divergence of opinion. On the other hand, confirmation of results in different species has served to strengthen certain conclusions.

Since the vitality of the mucosa is, under normal conditions, dependent upon secretion, circulation, and innervation, numerous theories for the pathogenesis of ulcers, involving a disturbance of one or more of these factors, plus others less subtle including those classified as unknown, have been proposed. Among the best known theories regarding the cause of the acute ulcer which developes into the chronic lesion are: (1) the acid-peptic, (2) mechanical, (3) vascular, (4) the gastric-specific and non-specific inflammatory, (5) the neurogenic, vascular spasm, hypermotility and secretion, (6) the nutritional, (7) the allergic, (8) the endocrine, (9) the metabolic - the action of various unknown metabolic factors, (10) other local factors diminishing tissue resistance, (11) unknown - constitutional.

Analytically it is clear that ulcers can be produced by the action of abnormal external destructive factors acting on the mucosa, or to a diminution in the normal resistance of the mucosa to injury, as well as in its normal healing properties, or to a combination of the above. In an attempt to classify the numerous methods of procedure for the production of ulcers, not a few of which involve a combination of factors, considerable overlapping may be anticipated. These methods have been discussed under the following ar-

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bitrary classification: (1) the acid-peptic, (2) the neurogenic, (3) the infectious, (4) the mechanical, (5) the vascular, (6) the nutritional, (7) the metabolic and endocrine.

I. THE ACID-PEPTIC FACTORS

The importance of gastric secretion to peptic ulcer has long been suspected, for ulcers are found only in that portion of the digestive tract which is exposed to the action of gastric secretion. Virchow, in 1853, (220) laid stress on the corrosive action of gastric secretion as a most important factor in the progress of the disease.

Many writers have raised the question: can acid alone injure the gastro-intestinal mucosa? Which is responsible for the ulceration, the acid or the pepsin? Matthes, in 1893, (138) studied this problem, using a Thiry-Vella loop. He perfused the loop with a hydrochloric acid solution and gastric juice. He produced superficial necrosis with the hydrochloric acid alone, but the most marked reaction occurred with the peptone free pepsin hydrochloric acid solution. He concluded that the peptones in the gastric juice combined with the free hydrochloric acid, and the reduction in the free hydrochloric acid was responsible for the reduction or absence of ulcerating power.

Most subsequent investigators have confirmed Matthes' observations that acid in physiologic concentration can damage the intestinal mucosa. Saitta (1900) (186), administered 3% hydrochloric acid by mouth and observed hemorrhagic erosions; however, after vagotomy the administration of the acid resulted in multiple ulcerations. Litthauer (1909) (131) produced ulcers by feeding hydrochloric acid after having caused an anemia by injection of pyrogallic acid. He also produced ulcers by administering hydrochloric acid after ligating the gastric vessels and excision of a corresponding piece of mucosa. Langenskiold (1904) (126) perfused isolated loops with pepsin and hydrochloric acid, with resultant ulcerations.

The acute experiments were somewhat uncertain. Smith (1914) (207) studied the relationship of bile to ulceration of the gastric mucosa. He studied mixtures of bile with and without acid and concluded that the presence of acid is necessary for the production of hemorrhagic erosions or ulcerations of the mucosa. Bolton (1914) (26) found that hydrochloric acid did not have any effect on the mucosa of the stomach under a concentration of 0.7%, but once a local lesion had been produced by other means, concentrations as low as 0.25% caused an increase in the size of the lesion and delayed healing of the ulcer. Rassers (1925) (171) introduced pepsin and acid into the stomachs of dogs, sacrificed the animals after one to three days' experimentation, and found profuse ulceration of the stomach. Dragstedt (1917) (46) McCann (1929) (142), and Dragstedt and Matthews (1933) (50) emphasized the role of acidity in the gastric juice almost to the exclusion of pepsin.

Mann and Bollman (1932) (135) emphasized the role of the acid factor as predominating in the development of ulcer. They administered 0.4% hydrochloric acid by continuous drip for eight hours per day, with the development of ulcers near the lesser curvature. They found that acid appeared to retard healing and to extend the ulcer.

Florey and Harding (1934) (70) studied the varying capacity of the intestinal mucosa to resist damage by acid. They found that the gastric mucosa was undamaged by N/10 HCl. The first part of the duodenum was damaged by this but withstood N/20 HCl. The jejunum was severely damaged by N/20 HCl. Bollman and Mann (1932) and others found a similar gradient of resistance to damage by gastric juice. It seemed likely to Florey and Harding that the production of an alkaline mucous secretion of the duodenum partially protected the mucosa from damage by acid, and experiments were conducted to determine whether the mucous secretion in the colon could play a similar role. Using N/20 HCl, on the basis of histological observations, the authors concluded that the mucous secreted by the goblet cells was incapable of preventing damage to the mucosa. They felt that their observations lent support to the view that the normal secretion of Brunner's gland protects the mucosa from damage by the acid gastric juice by virtue of its mucoid consistency and contained alkali; and to the suggestion that malfunctioning of these glands may be primarily responsible for duodenal ulcers.

Matzner (1936) (140) produced ulcers in rats by feeding pepsin and hydrochloric acid. In acute and chronic experiments reported by Schiffrin and Warren (1942) (195) perfusion of a segment of the gastro-intestinal tract with pepsin in an acid medium produced more severe ulcerations than perfusion with acid alone. The maximum ulceration occurred with pepsin when it was employed in a medium having a pH within optimal range for peptic digestion. The duodenum of the cat, in the absence of biliary and pancreatic secretions, was more susceptible to the action of acid alone than was either the jejunum or ileum.

Kolouch (1945) (124) obtained gastric juice from pouches which had been stimulated with histamine, dropped it on the mucosa of the antrum or pylorus of dogs, and obtained injuries greater than when HCl alone was used.

In a group of experiments, the influence of hydrostatic pressure on the proteolytic activity of pepsin and other enzymes in the formation of ulcers was reported by Driver and his co-workers. In one experiment (55) small intestinal loops were used, and exposed to a solution of 0.1% pepsin in N/10 HCl under various hydrostatic pressures. In all cases where pressure was employed, perforation occurred, the damage was progressively worse as the pressure was increased and concomitantly the perforation time was progressively reduced. It was suggested that the pronounced effect of hydrostatic pressure on ulcer formation might be due to three factors: (1) mechanical

stretching, (2) decreased blood supply, (3) increased permeability of pepsin. With regard to this last factor, Driver (1943) (57), by using various chemical agents which affect the permeability of the mucosa, was able to increase the incidence of ulcers over controls.

In a study of the effect of various proteolytic enzymes under a hydrostatic pressure of 90 centimeters of water, Driver (54) reported the following: the proteolytic enzymes trypsin and erepsin produced necrosis of the intestines of dogs, but demonstrated a lesser degree of activity than did pepsin and rennin. Neither steapsin nor amylopsin caused necrosis under the above conditions. Chappell (1947) (33) observed that increased intra-abdominal pressure inhibits the perforations due to pepsin solutions under hydrostatic pressure, but seems not to inhibit the severity of the necrosis.

In studying the effect of varying this concentration of pepsin, Driver (1945) (56) found that the percentage of pepsin employed was apparently not a factor in the degree of the digestion of the mucosa, since there seemed to be as much damage with one concentration as with others. The more distal loops of gut used in these experiments seemed to be more susceptible to the action of pepsin-hydrochloric acid solution than the proximal segments. N/10 HCl alone produced about one-third as much damage as pepsin plus HCl.

The role of pepsin and hydrochloric acid in the production of peptic ulcers was analysed in a careful experiment by LeVeen (1947) (129). Experimental ulcers were produced in the small bowel of dogs by irrigation with acid-pepsin solutions of increasing acidity. Evidence was presented from an exclusive experiment to show that this effect of acid was dependent upon its enhancement of pepsin action rather than injury by acid. The author concluded that the experimental facts observed lend little credence to the theory that acid injures the cells and makes them more susceptible to peptic digestion.

Grossman (1947) (85), in an editorial comment, presented evidence which disagreed in part with the conclusions of LeVeen. Using an isotonic solution of dilute HCl which was permitted to drop on exposed jejunal mucosa, it was found that in every case histologic study of the area of blanching revealed unmistakable cell damage microscopically. The available evidence strongly indicates that acid alone, without pepsin, can damage intestinal mucosal cells. If this is so, then the ulcerogenic action of gastric juice cannot be ascribed solely to its peptic activity. On the other hand, there is little question that pepsin enormously increases the injurious effects of acid.

HISTAMINE

Ulcers have been produced in the stomachs of dogs, cats, rabbits and other animals by the continuous administration of histamine, and it has been concluded by a number of workers that the "histamine ulcer" is due to the continuous secretion of acid: however, this has not been established as the sole factor because as Ivy (112) and others have pointed out, doses of histamine have been used which may exert a local angiotoxic effect on the mucosa. Variations in the local vascular status of the stomach, and its influence on the production of "histamine ulcers" have also been studied by a number of experimentors.

Bückner, Siebert and Malloy (1928) (28) produced acute ulcerations in the rat by subcutaneous injections of histamine. Bürkle de la Camp (1929) (30) and Flood and Howes (1934) (68) showed that the healing of acute ulcers produced by the injection of silver nitrate beneath the gastric mucosa of dogs was markedly delayed by repeated injections of histamine. Orndorff, Bergh and Ivy (1935) (165) tried to produce ulcers in dogs with histamine, giving two mgm. every two hours subcutaneously. No ulcers were produced, but four dogs showed superficial ulcerations.

Walpole and Wangansteen (1940) (221), in a preliminary paper, reported on the production of acute ulcers in the stomach (antrum) or duodenum by the intramuscular injection of histamine in a beeswax mixture. In a more extensive report, these workers (1942) (100), employing various animals as dogs, guinea pigs, cats, chickens, ducks, swine and woodchucks reported that ulcers were produced without difficulty by means of daily implantations of histamine in beeswax, in all the animals except the monkey and the rabbit. It was possible to produce ulcers regularly in rabbits by this technique upon discarding the cellulose pulps of cabbage, carrots and lettuce, and feeding only the juice that went through the press. By this means it was possible to get the rabbits' stomachs empty, permitting the acid-peptic digestive mixture the opportunity to attack the wall directly.

Roth and Ivy (1944) (181) administered histamine intravenously to anesthetized cats without change in the gastric mucosa. But if caffein was injected intravenously or if lavage of the stomach was altered with histamine, large areas of epithelial desquamation, multiple bleeding erosions and ulcerations of the gastric mucosa were observed. Since both caffein and histamine appear to stimulate the flow of an acid gastric juice and cause vaso-dilatation, and since histamine alone did not induce ulceration in this acute experiment, then caffein presumably provides an additional factor which contributes to the decreased resistance of the mucosa.

It was observed by Baronofsky and Wangansteen (1945) (11) that perforated ulcers may be brought about quite regularly in rabbits by the production of chronic arterial spasm achieved by the implantation of epinephrine in beeswax, when accompanied by the simultaneous administration of histamine in beeswax. In the rabbits receiving histamine alone, no ulcers appeared. Repeated tests with adrenalin in aqueous form failed to reveal any definite stimulation of gastric secretion in Heidenheim and Pavlov pouch dogs. Local spasm evoked by epinephrine and pitressin produced local areas of ischemia which then became

susceptible to the digestive action of the gastric juice. The depressant action of pitressin was also verified on pouch dogs.

In an experiment performed on dogs and rabbits by Baronofsky and Wangansteen (1945) (9), partial obstruction to the venous outflow of the stomach was produced by ligation of the splenic vein and other vessels and by portal obstruction. This procedure increases the weight of the stomach and an edema of the entire stomach wall is seen microscopically. "Histamine ulcers" are more readily induced in these animals than in normals. In the rabbit, normally resistant to histamine-in-wax injections, ulcers are readily produced following obstruction to the venous outflow.

Experimental production of ulcer and/or erosion by fracture or curettement of bone was studied by Wangansteen, et al., (8, 144) in various animals. Several of the guinea pigs developed ulcerations or erosions, none of the cats developed lesions, and half the dogs developed gastro-duodenal lesions. Three possible explanations were proposed by the authors: (1) histamine effect from the fracture site, with stimulation of gastric secretion, (2) fat embolism, (3) a combination of these two factors. Using intact dogs, gastric aspirations were carried out before and after drill holes through the humerus were made. No significant difference in gastric secretion was observed in samples taken before and after bone trauma. In dogs with gastric pouches, such procedures (145) as well as intravenous injection of fat failed to evoke evidence of stimulation of gastric secretion. Therefore it was concluded that the histamine effect was not a primary cause of the observed erosions or ulcerations in animals.

To test the influence of fat embolism, fat was injected intravenously on rabbits, cats, dogs and guinea pigs, (10). Ulcerations or erosions were observed following a single intravenous injection of fat, in a number of animals. In rabbits, the injection of fat alone resulted in no ulcerations; but combined with histamine-in-wax injections, ulcerations were produced in all cases. This is significant in that rabbits are normally resistant to ulcerations by histamine injections alone. Results show that fat emboli released in the bloodstream (9) may occlude the end vessels in the gastric or duodenal mucosa, causing areas of local ischemia. Thus these areas become more susceptible to the acid peptic digestive activity of the gastric juice. Even though the intravenous fat does not stimulate or augment gastric secretion, the resultant anemic areas become less resistant to injury and digestion by the acid-peptic juice than the normal mucosa.

In experiments carried out on dogs and rabbits, the effects on ulcer formation of burns produced by immersion in hot water and injections of histamine-in-beeswax given before the burns were studied. The experiments showed (75) that burns abet the ulcer diathesis, i. e., ulcers are produced more readily and quickly with histamine in the presence of gastro-intestinal congestion resulting from experimental burns, in both dogs and rabbits. In a further experiment (76) evidence is presented to show that there is a close correlation between the hemoconcentration following burns and the occurrence of gastro-duodenal congestion, erosion, and/or ulcers: moreover, there is a direct relationship between the two. The incidence and severity of the ulceration produced by the hemoconcentration is markedly increased when histamine-in-beeswax administration accompanies the burns. The gastro-intestinal abnormality following burns, even when accompanied by histamine administration may be prevented by avoidance of hemoconcentration of burns by proper therapy.

A number of experiments have been carried out on the prevention of "histamine ulcers" by medical and surgical means. Friesen, Baronofsky, and Wangansteen (74) found that benadryl failed to alter the gastric secretory response to histamine stimulation in pouch dogs, and failed to protect against histamine produced ulcers in dogs. Crane, Lindsey and Dailey (38) found that treatment with benadryl does not prevent histamine induced ulcers in guinea pigs. None of the anti-histamine drugs so far tested have prevented ulcerations, nor have any of them shown a significant inhibiting effect on the gastric stimulatory action of histamine (87).

Fast, Friesen, and Wangansteen (61) have found that the Sippy regimen protects against the ulcer provoking tendency of histamine in experiments on dogs.

A group of experimental studies were undertaken by Wangansteen (222) and his workers to determine which type of surgical procedure would best protect against the formation of histamine induced ulcers and the various factors involved. A study of the length of the duodenal-jejunal loop and its relation to the occurrence of stomal ulcers in animals receiving histamine, and in those not receiving it, were also carried out. (31, 147, 223). With the short loop, gastro-jejunal ulcer occurs infrequently (9.1%); whereas with the long loop it is the rule (83.3%). The mechanism by which the length of the loop affects the frequency of occurrence of stomal ulcers is not so apparent. Various operations were employed in the attempt to separate and study the effect of the "secretion" factor (stimulation by HCl of pancreatic juice) from the "distance" factor and the "sensitivity" factor of the intestinal mucosa, but they were not too successful. It was concluded that the "secretion" factor cannot be completely separated from the "distance" factor, and that the long afferent duodenal-jejunal loop predisposes to occurrence of stomal ulcers in any gastric operation carried out on the Bilroth II plan of procedure.

A series of experiments was carried out to study the effect of variation in the amount of stomach sacrificed on the occurrence of histamine provoked ulcers (7). In these experiments, 25%, 50% and 75% of the stomachs were resected. It was only when 75% of the stomach was resected that stomal ulcers were

not provoked with histamine, and that it did not make any difference whether the Bilroth I or II plan of procedure was employed. The 75% resection carried out on a Bilroth II plan, employing a short afferent duodenal loop in which the antral mucosa and the lesser curvature of the stomach are excised meets the requirements of a satisfactory operation for ulcers, according to these investigators.

It was observed that (6) vagotomy, with and without gastro-jejunostomy failed to protect against ulcer and erosion (gastric and/or jejunal) produced by chronic histamine action in the dog, cat and rabbit.

SURGICAL METHODS

In order to study the effect of pure gastric juice on the formation of ulcers, the resistance of the tissues to digestion, the influence of the digestive juices and the nature of the physiological interrelationship of the juices, a great variety of operative procedures has been devised.

1. Bile exclusion. Bile has been excluded from the intestinal tract in experimental animals in a number of ways and its influence as a factor in peptic ulcer formation studied. It has been diverted to the outside by various types of external fistula, diverted into the pelvis of the kidney from which it passes out into the urine, diverted into the lower intestine or colon, and by completely and permanently occluding the bile ducts (18). Gundermann (89) after simple ligation of the common duct observed hemorrhages and ulcerations of the stomach and duodenum as well as symptoms of hepatic dysfunction. Kapsinow (117) excluded bile from the digestive tract by implanting the fundus of the gall bladder into the pelvis of the right kidney and then ligating and dividing the common duct. In addition to inanition and tarry stools at autopsy, single and multiple ulcerations developed in 17 of 43 animals. Beaver (14) on the other hand reported negative results after cholecystogastrostomy and ligation of the common bile duct. Bollman and Mann (22) reported perforating ulcers following partial hepatectomy, true Eck fistula and ligation of the common duct. Complete obstruction of the bile ducts with resultant jaundice and hepatic cirrhosis led, they observed (23), to the development of duodenal ulcers in the majority of animals so prepared.

Dragstedt (47) has prepared a free flowing type of external biliary fistula, and the dogs so prepared survived from six to 15 months showing, at death, no evidence of ulcer in the stomach or duodenum. He suggests that it may be of considerable importance that no obstruction to the free flow of bile exists with this type of fistula, that ascending infection does not occur, and that the liver remains grossly and histologically normal. It is possible that the varying incidence of ulcers reported after external biliary fistula by the Rous and McMaster technique or after anastomosis of the gall bladder to the ileum, colon, or the pelvis of the kidney following occlusion of the common bile duct may be due in part to factors of partial obstruction or ascending infection. The probability that damage to the liver is important in the genesis of some of these ulcers resulting from biliary fistulas is supported by the findings of cirrhosis of the liver in some preparations (22), and by the fact that chronic duodenal ulcers occasionally appear in animals with Eck fistula as well as after the administration of cinchophen (209).

2. Exclusion of pancreatic juice. Pancreatic juice has been excluded from the duodenum of the dog by various types of operative procedure such as differing types of external pancreatic fistula, implantation of the ducts into the lower intestine, ligation of the ducts, and pancreatectomy. These procedures have produced widely divergent results.

Jona, (115) after ligating the pancreatic duct in eleven animals, found ulcers in the stomach, duodenum and jejunum, which he believed to be due to lack of neutralization of the acid chyme. Gallagher (78) observed delayed healing of acute traumatic ulcers of the duodenum after ligation of the pancreatic duct. Partial exclusion of the pancreatic juice has been produced by cannulating or implanting the lower larger pancreatic duct of the dog into the abdominal wall. In such animals, ulcers rarely develop. Elman (59) cannulated this duct by the Rous and McMaster technique after first ligating the other duct, thus securing a much larger volume of pancreatic juice and the development of duodenal ulcers.

The failure of many experimentors to obtain ulcers of the duodenum by producing an external fistula of the lower duct is undoubtedly due to the fact, according to Dragstedt (47), that in this preparation the major portion of the pancreatic juice still finds its way into the duodenum. This is illustrated by the occurrence of ulcer in almost 100% of animals from which the entire secretion is drained to the outside by the type of fistula described by Dragstedt (51). Dragstedt (47) has performed more than 100 such fistulas. These animals die rapidly of dehydration and acidosis, unless the sodium lost in the pancreatic juice is replaced by parenteral injection. When this is done life is greatly prolonged, but almost invariably, a progressive ulcer of the duodenum develops which causes death from hemorrhage or perforation. The occurrence of these ulcers may be prevented or at least delayed by the oral administration of calcium carbonate and powdered bone meal, but so far the author has not been able to cure an ulcer so formed.

Permanent occlusion of the pancreatic ducts results in atrophy of all but the islet cells. In such animals, Dragstedt (47) reports the occurrence of ulcers in 29%, which agrees with the reports of others. On the other hand, in over 300 pancreatectomized dogs studied by Dragstedt over a prolonged period of time, only four presented duodenal or gastric ulcer. These animals were fed well balanced diet and vitamin supplements but were not given alkali in any form. The question was raised: why does ulcer develop in the dog with total pancreatic fistula in 100% of the cases, while the animals whose pancreas has been removed

remain almost immune? These results suggest that the problem is not entirely one of failure of neutralization of the gastric acid by the sodium bicarbonate of the pancreas.

3. Effect of exclusion of duodenal juice from the upper intestines. Bickel (21) extirpated the duodenum with production of ulcerations. Dragstedt (49) excised the duodenum and excluded both the bile and pancreatic juice without development of ulcers. On the other hand, Mann and Kawamura (136) performed a duodenectomy, the jejunum being anastomosed to the pylorus, and the bile and the pancreatic ducts were implanted into the jejunum with the development of ulcers in 20% of the animals. The authors believed this to be due to the elimination of the protective mechanism of the duodenal mucosa and secretion; however, the possibility exists that the implantation of the bile ducts may have caused some obstruction and damage to the liver.

Summary of the data (47) would indicate it is safe to conclude that absence of pancreatic juice, bile and duodenal juice, or possibly anyone of these secretions, may be expected to cause a progressive perforating ulcer of the duodenum. The nature of the protective actions of these secretions is not entirely settled. It is likely that the neutralization of the hydrochloric acid by the sodium bicarbonate of these secretions (which is greatest in the pancreatic juice) may play a part in this protection.

4. Effect of the combined exclusion of bile and pancreatic juice from the upper intestines. A number of authors, Bickel (21), Exalto (60), Langenskjold (126), Kehrer (119), Mann and Williamson (137), have demonstrated successfully that exclusion of bile and pancreatic juice from entering the duodenum at the usual site was an effective means of producing ulcer. Mann and Williamson (137) observed that after transplantation of the bile and pancreatic ducts there was a variable loss of weight and the development of ulcers in 10 of 31 animals. Following duodenectomy and the transplantation of the bile and pancreatic ducts to the terminal ileum, it was found that chronic ulcers developed in seven of ten animals; However, it was difficult to maintain their nutrition. The above operation was modified to improve the mortality, so that the duodenum was made to drain its own secretion and that of the liver and pancreas at a considerable distance from the pylorus. It was found that 14 of 16 animals developed ulcers, all of them of the subacute or chronic variety. These lesions were located in the intestines a few millimeters distal to the pyloric mucosa: some were multiple, but as a rule they were single. The ulcers developed usually within one or two months after operation, were from four to 15 mm. in diameter, and penetrated to various depths. A grey covering first appeared over an area of the mucosa where killed coagulated cells were present. Hemorrhage occurred between the adjacent tubules. As the mucosa disappeared, leucocytic infiltration developed and the process penetrated to the muscularis mucosae. Perforation occurred in from forty-eight to sixty hours; chronicity was established in three weeks, and the lesion was the same at the end of five months as at the end of one month. Further observations by Mann and Bollman (135) and others have shown that this type of operation resulted in ulcers in 95% of cases.

Considerable experimental data has accumulated on the Mann and Williamson dog. Much experimental work by Ivy (113) and others (155, 69, 43, 143, 139, 142) have shown that there are at least three factors in this experimental ulcer: 1) the acid factor, probably most important, 2) the nutritional factor, since diversion of pancreatic juice and bile to the lower part of the ileum disturbs intestinal digestion as well as neutralization of acid chyme, 3) the increased sensitivity of the jejunal mucosa to gastric secretion as compared to that of the duodenal mucosa with an increased gradient of sensitivity the greater the distance from the duodenum. In addition, Mann and Williamson (137), McCann (142), Morton (155) and others have stressed the mechanical factors, such as the size and force of the stream impinging on the jejunal muscosa. The question of the factor of spasm of the muscularis of the jejunum in the Mann-Williamson dog was studied by Steinberg and Starr (211). They prevented spasm of the jejunum when they stripped the muscularis from the jejunum at its anastomosis with the stomach. Ulcer was subsequently absent from the stripped region, but readily formed at the first portion of the jejunum having an intact muscle. Fauley and Ivy (65) repeated this experiment with a modified technique. Although the previous studies were not invalidated, they demonstrated that a local spasm was not essential to the production of ulcer near the anastomosis.

As pointed out by Dragstedt (47), in all of the experiments in which pure gastric juice from an isolated pouch of the stomach is permitted to flow into the lower intestine, the ulcer forms in the intestinal rather than in the gastric mucosa. Since the exposure is similar, one must conclude that the gastric mucosa has the greater resistance to digestion. That this protective capacity is not absolute has been demonstrated clearly by means of completely isolated stomachs in which the secretory vagus innervation has been preserved. If alkalis and dehydration incident to the total loss of gastric juice are compensated for by intravenous injections of adequate salt solution these animals survive in good condition for many months. In the great majority, punched out ulcers with hemorrhage occur in the mid-portion of the stomach. The preservation of the secretory fibres of the stomach seems to be a matter of some importance, since in the same preparation, after vagus section, no ulcers were formed (52).

Schmilinsky (194) suggested the placement of the afferent duodeno-jejunal loop in the Bilroth II type of gastric resection back into the stomach in such a manner that all the duodenal contents drained back into the stomach for the neutralization of the gastric acidity. McCann (142) modified the Mann-

Williamson operation by draining the duodenal secretions into the fundic portion of the stomach, rather than into the distal part of the ileum, under the same assumption that these alkalis might control the acid factors in the stomach and thus prevent the formation of ulcers which develop after the total elimination of the alkalis. However, he found, following the operation, typical jejunal ulcers in approximately 80% of a series of twenty-six dogs.

A number of investigators (113, 223, 225) have repeated the McCann experiment with indifferent results. None were able to confirm the observations of a high incidence of gastro-jejunal ulcers following complete drainage of the duodenal loop back into the stomach.

To clarify the conflicting results of the effects of the McCann operations, a short duodenal loop and a long duodenal-jejunal loop were employed in two series of dogs studied by Wangansteen (222). The differences in the literature may be explained on the basis of the length of the afferent duodenal loop. With the short loop, gastro-jejunal ulcers occur infrequently (9.1%), whereas with the long loop it is the rule (83.3%). The mechanism by which the length of the afferent loop affects the frequency of occurrence of stomal ulcers is not so apparent.

Besides mechanical factors, Wangansteen (223), Kesavalu and Mann (123) have suggested that the constant secretion of the duodenal loop might stimulate or enhance the secondary or gastric phase of gastric secretions interminably.

In dogs operated upon by the Mann-Williamson procedure, and in animals fed cinchophen, a number of liver function tests were performed to see whether there was any derangement of liver function (173). On the basis of these tests it was concluded that the operation per se does not cause any detectable disturbance in liver function. If liver damage has anything to do with the etiology of ulcer in the dog, it must be of a purely specific type.

Because the Mann-Williamson preparation has resulted in the rather uniform production of chronic ulcers, it has been extensively utilized by a number of investigators to study a great variety of therapeutic measures.

In a study (66) on the use of aluminum hydroxide gel, it was found that this drug failed to prevent post-operative jejunal ulcers, and it was suggested that this might be due to an interference with the absorption of phosphates. This was substantiated in a later work (62) where it was found that aluminum hydroxide in relatively large doses interferes with phosphorus absorption, and the lack of benefit was ascribed to a relative phosphorus deficiency.

Studies in the use of aluminum phosphate gel (62) in Mann-Williamson dogs demonstrated more favorable results with aluminum phosphate than with any other therapeutic agent previously used, preventing the formation of ulcers in 20 of 23 dogs and promoting the complete healing of previously developed ulcers in nine of 10 dogs. While gastric mucin (166) was found to be better than alkali and aluminum hydroxide gel, it was found to be inferior to aluminum phosphate.

Fauley and Ivy (64) observed the prevention of jejunal ulcers following fundusectomy. They also found that Mann-Williamson dogs developed lesions more readily on a restricted diet than on a full diet. Even the lesions which had developed tended to heal if adequate diet was again given.

During the past ten years, several groups of investigators have studied the influence of chalone or hormonal agents in the treatment or prevention of experimental ulcers. These have included various extracts from the first part of the small intestine of hogs, urinary extracts from normal humans and animals, and urine of pregnant humans and animals. Ivy and his group have conducted extensive experiments on the use of enterogastrone. Enterogastrone (112) is an autocoid or substance which is produced by the intestinal mucosa in the presence of adequate concentrations of fat and sugar in the chyme and which inhibits gastric secretion and motility. This substance, given parenterally, inhibits or abolishes the gastric secretory response to histamine. Ten Mann-Williamson dogs treated daily with an extract of dog muscle prepared by the same method as the enterogastrone preparation developed jejunal ulcers in four months (92). The development of jejunal ulcer was prevented in 76% of the 25 Mann-Williamson dogs which were treated daily for one year with the enterogastrone preparation administered intravenously (111). The therapy was discontinued after one year. The withdrawal of therapy was not followed by ulcer formation. Two of the eleven surviving animals developed ulcer from 18 to 28 months after cessation of treatment. Eight dogs died from miscellaneous causes and one dog is still living and in excellent condition nearly six years after operation (82, 111). This period of "immunity" following the cessation of treatment is remarkable in view of studies in which, when ulcer was prevented in Mann-Williamson dogs by the administration of aluminum phosphate gel, ulcer developed in an average of 2.4 months after cessation of treatment (62).

Mechanism of the protection: it was found (111) that the untreated Mann-Williamson dogs manifest a long continued hypersecretory response, i. e., they secrete longer in response to alcohol stimulation. Those dogs injected with and protected by enterogastrone respond like normal dogs to alcohol, and do not respond hyper-continuously like the untreated control animals. Studies on pepsin output in response to histamine show that the normal dog and the enterogastrone treated dog secrete the same amount of pepsin. The protection afforded cannot be explained on the basis of the action of enterogastrone in inhibiting gastric secretion. It is suspected that the therapy increases the resistance of the mucosa, however the

true nature of the agent concerned cannot be defined at present.

Sandweiss and his associates (188, 189, 192, 15) have observed similar long-lasting protection against recurrence of jejunal ulcers in dogs 2 1/2 years after the cessation of treatment, in which they employed an extract of human urine injected parenterally. This action has been attributed to the presence of a principle in the urine called "anthelone," the effect of which is to produce fibroblastic proliferation, vascularization and epithelialization of the intestinal mucosa. The precise relation of "anthelone" to enterogastrone is not clear. Human and canine urine contain materials that suppress gastric secretion and motility, and which, according to Sandweiss (189), are in addition to "anthelone" the anti-ulcer factor. Urogastrone is essentially an extract of urine which depresses gastric secretion and motility (83, 160). The same principles which have been ascribed to anthelone seem, according to Necheles (159), to be present in both enterogastrone and urogastrone. Whether enterogastrone and urogastrone are alike or not has not been settled, for there are differences in some of their physical and chemical properties. It has been suggested that these differences may be due to differing impurities contained in the preparations which may affect the reaction. Another argument of dissimilarity between the two substances is that, following enterectomy, the urine of animals still contains urogastrone. It may be, however, that urogastrone is stored in the body and excreted so slowly that the enterectomized animal does not live long enough for the store to be exhausted. Therefore, one cannot exclude the possibility that the intestinal mucosa may be the source of urogastrone. Anthelone, on the other hand, may be different from the other two; i. e., the gastric inhibitory and ulcer healing or preventative effects are not contained in one principle. It seems that the effect on the integrity of the gastric and upper intestinal mucosa is common to all three, enterogastrone, urogastrone, and "anthelone."

A number of studies have been made by Sandweiss (189, 190, 191) on the relation of the endocrine glands, particularly the anterior pituitary, "anthelone" and ulcer. In a study of the relation of the endocrine glands to the gastric secretory depressant in urine (urogastrone) Kaulbersz, et al., (118) reported that urogastrone (gastric secretory depressant in normal urine) is also present when the ovaries and thyroid are removed; however, if the hypophysis is removed, the depressant is diminished, if present at all. In the majority of the experiments, the secretion was increased in the urine from the hypophysectomized animals. The preliminary data were considered indicative of a relationship between the pituitary gland and gastric secretion, and suggested that disturbance in pituitary gland factors comes into play that augments the action of gastric secretion and stimulates and contributes to ulcer formation.

The "Shay rat" has been used to test enterogastrone and urogastrone. In the Shay procedure (200) the rats are fasted for 48 hours, then the pylorus is ligated under ether anesthesia and the rats are not fed subsequently. Marked ulceration occurs in the rumen in from seven to nine hours after operation. Pauls, Wick, and MacKay (169) administered anti-ulcer material from human urine intravenously at the time of operation, with the reduction or prevention of ulcers. In another experiment Wick, et al., (228) obtained, by means of a carbon-acetone method, a preparation of human urine containing a significant amount of anti-ulcer factor. The chemical relationship between urogastrone, enterogastrone and the urinary "carbon-acetone" material, and the proof that the carbon-acetone produced extract is due to a single chemical entity, must await further study. The charcoal-acetone preparation from human urine, given at the time of pyloric ligation, prevented the development of gastric ulcers. The mechanism of the anti-ulcer effect is unknown. It may be due to a reduction in gastric secretion, impaired peptic activity of this juice, or an enhancement of the resistance to ulceration which is inherent in the gastric mucosa.

Grossman, Dutton and Ivy (86) found that treatment with enterogastrone concentrates (100 mgm.) given by daily subcutaneous injections did not prevent histamine induced ulcers. As this dosage had been found effective in preventing ulcers in Mann-Williamson dogs, the authors concluded that factors concerned in the pathogenesis of this type of ulcer were different from those operating in the former.

A group of ulcer patients have been receiving injections of enterogastrone six days a week with encouraging results (112, 82). Urogastrone and anthelone have also been administered, both to normal individuals and to patients with duodenal ulcers. In recent papers, the use of a polyamine formaldehyde resin (Amberlite IR-4) was reported to be effective in neutralizing acidity of hydrochloric acid solution and gastric juices in vitro, and its use in peptic ulcerations was reported. Chronic experiments (203) using this material orally in rats have revealed that the overall toxicity of this resin, for rats, was negligible.

II. Neurogenic Factors

Since the early writings of Rokitansky (174) and his school who hypothesized that ulcerations of stomach and duodenum might be caused by "morbid conditions" of the vagus, extensive investigation on the neurogenic origin of peptic ulcer has followed. This has, in general, followed two lines: (1) experiments on the brain and (2) experiments on the peripheral nerves.

The cranio-sacral and thoracic-lumbar systems which innervate the stomach and duodenum, have an antagonistic visceral effect. A number of reports have been made on experiments performed on the brain. As early as 1845, Schiff (193) found that unilateral lesions involving the optic thalamus and adjacent cerebral peduncles in rabbits and dogs often produced gastromalacia and perforations. These findings were con-

firmed by a number of early investigators, as Claude Bernard, Brown-Sequard and Epstein. Punctures in the hypothalamic region (29) have produced gastric ulcers. Keller, Hare and D'Amour (121) produced acute lesions of the gastro-intestinal tract by producing intraventricular hemorrhage or by section of the brain at the level of the chiasm. Hoff and Sheehan (103) produced multiple hemorrhagic erosions of the mucosa of the stomach by lesions involving the tuberal area in monkeys. This was confirmed by Keller and D'Amour (120) and they showed, in addition, that the occurrence of hemorrhage into the mucosa was not prevented by section of the vagus fibres, and that ulceration was not prevented if the sympathetic fibres were removed. Watts and Fulton (224) found that gastric and duodenal ulcerations in monkeys were produced as a result of extensive hypothalamic damage. They explained these lesions as being principally due to ischemia of the mucosa brought about by the vasoconstrictor fibres.

Beattie (13) stimulated animals directly in the region of the tubercle centres and obtained increased peristalsis and secretion, and if the stimulation was long-continued, hemorrhagic erosions in the mucous membrane near the lesser curvature were obtained. After vagal section, these effects were not procured. The question, however, whether the secondary peptic ulcers have been due to parasympathetic (vagal) stimulation or sympathetic paralysis is, at present, not clear, but awaits more precise information.

Cushing (40) injected various drugs intra-ventricularly in man, with very interesting results. Pituitrin (surgical) caused prompt acceleration of motility, retrograde peristalsis, with vomiting. These effects were checked by atropine. Pilocarpine (2 mgm.) caused prompt activation of motility, spasm of pylorus, retrograde peristalsis with vomiting, also perspiration, cutaneous flush, and fall in temperature. These reactions were checked by atropine. These two produced their effects by assumption of the stimulation of a center for parasympathetic discharge. On the other hand, adrenalin injected intramuscularly produced an almost immediate cessation of all visible movements for twenty minutes or longer. Pituitrin (surgical) produced a similar effect and cutaneous pallor; and pilocarpine (12 mgm.) produced a definite diminution of motility with moderate sweating. A series of cases of gastric perforations following cerebellar operations were presented by Cushing, which he believed were due to irritative effects on vagal centers; the action was due to spasmodic contraction of the stomach musculature and probably supplemented by accompanying local spasms of the terminal blood vessels with small areas of ischemia or hemorrhagic infarction. Tedeschi (215) found gastric lesions in 7% of rats submitted to head trauma. A correlation was observed between the severity of the trauma, the cerebral damage and the occurrence of gastric alterations which showed a tendency to prompt and complete healing in the surviving rats.

Many contradictions have appeared with results of peripheral lesions. Dalla Vedova (41) and Durante (58) operated on the splanchnic nerves and produced gastric lesions, and Mann (133) and Ivy (108) produced ulcers following removal of the adrenals. Durante, extending the work of Vedova, showed that resecting the greater splanchnic nerves resulted in slight transient changes in the stomach, but section of the median splanchnic nerve, which stimulated the secretion of adrenalin, produced hemorrhagic and spastic lesions. The hemorrhagic lesion, due to small injury of a blood vessel, resulted in an acute ulcer which healed by a scar, while the spastic lesion, due to a spasm of a blood vessel, became the starting point of a chronic peptic ulcer. Observations on suprarenalectomized animals revealed petechial hemorrhages and erosions of the gastric and duodenal mucous membranes with ulcers occurring less frequently.

Gundelfinger (88) after extirpation of the coeliac ganglion, produced gastric lesions. Dalla Vedova (41) had observed erosions and hemorrhagic lesions in an earlier report. Latzel (127) and others have reported failure to produce them after extirpation of the coeliac ganglion. Beazell and Ivy (16) observed that chronic gastric ulcers followed bilateral vagotomy in the rabbit, and less frequently in the dog, when these were fed on a rough diet.

Variable results following vagus section have been reported by a number of writers, some reporting ulcerations and others none. Ivy (108) has shown that dogs dying immediately after section of the vagi and splanchnics not infrequently showed petechial hemorrhages of the pyloric and duodenal mucous membranes; but in dogs dying or killed from one week to four months after double vagotomy, splanchnectomy with extirpation of the coeliac ganglion, no gastric or duodenal lesions were found.

Peripheral stimulation of the vagus has produced gastric ulcers in experimental animals. Keppich (122) produced gastric ulcers in rabbits by electrical stimulation of the vagi. Stahnke (208) stimulated the vagi in dogs near the cardia by placing the electrodes in the lumen of the lower esophagus, with resultant hypermotility, pylorospasm, and chronic gastritis, and ultimately erosions.

Vagal stimulation causes increase in secretion and motility, whereas sympathetic stimulation gives the reverse effect. Vagal paralysis diminishes secretion and motility. However, gastric acidity may return in months or years after bilateral vagotomy. Sympathetic paralysis increases secretion and motility by releasing the check of the vagus.

In experiments performed on rabbits, Aschoff (4) reported that ulcers produced by branding healed more slowly when atropine was given. In a second series of experiments, he found that vagus section also exhibited a restraining influence on the healing of ulcers. He believed the loss of tone and decrease in contractility contributed to the diminution of the healing tendency.

In an interesting study by Westphall and Kukuck (226) the stomach of the dog was slit open and the distal end of the cut vagus electrically stimulated. After stimulating for a few minutes, there was an increase in the gastric folds and activity. After half an hour of stimulation, there was a hyperemia of the mucosa. Microscopically there was seen early an increase of secretion and cells, and later small hemorrhages in the corpus due to edema and destruction of the epithelium producing an erosion. In the antrum, erosions that are deep develop, which are different in character from those of the corpus. In another group of animals, the stomach was examined during intravenous adrenalin injections. The mucosal folds became smaller and anemic; after a few minutes a hyperemia of the corpus with fine point edema of the surface developed.

Dragstedt (47) has pointed out that in the completely isolated stomach in which the vagus innervation remained intact, ulcerations occurred in the great majority. On the other hand, in the same preparation after vagus section, no ulcers were found. In three groups of dogs studied by Berg (19, 20) frequent injections of pitressin were given, one group having had a previous bilateral vagus section, and a second group a bilateral sympathectomy. Lesions of the stomach were obtained in a greater number of cases, and were more extensive, in the vagotomized than in the normals. In the sympathectomized animals no gastric lesions were seen. These findings were correlated with the greater severity of the reaction observed following the injection of pitressin in the vagotomized and normal groups as compared with the sympathectomized animals.

In the Shay rat, Shay et al. (200) have reported that atropine will prevent ulcerations which otherwise uniformly appear. It has been shown more recently (96) that bilateral transabdominal section of the vagus nerves will also prevent ulcer formation in the Shay rat. Bilateral vagotomy (16) supra- and infra-diaphragmatic, with and without gastro-jejunostomy failed to protect against ulcer or erosion (gastric and/or duodenal) produced by chronic histamine action in the dog, cat and rabbit.

III. INFECTION

Infection has commanded the interest of many workers in the pathogenesis of ulcers. Lebert (1857) (128) injected pus intravenously into animals with resulting pyemia and acute gastric ulcers. A number of the early investigators injected various organisms intravenously with variable results, though many reported the production of acute gastric erosions. In general, the experiments followed two routes of administration; (1) oral ingestion and (2) intravenous injection of bacteria. Türck (216, 217) reported ulcers in dogs after feeding B. Coli. communis obtained from the feces of an ulcer patient. Singer (205) produced lesions in the pre-stomach of rats by feeding a diet of bread and rat feces. Rosenow (177, 179) could not demonstrate the formation of ulcers after the oral administration of streptococcic strains which he used to produce lesions by intravenous injection. Ivy (110) and others have applied streptococci locally without the production of ulcers.

More constant results have followed the injection of organisms into the blood stream Steinharter (212) reported acute gastric and duodenal ulcers following intravenous injections of a staphylococcus isolated from an acutely inflamed appendix. Hoffman (104) injected a culture of a coma shaped bacillus obtained from the gastric contents in a case of ulcer and obtained lesions of the stomach and duodenum in guinea pigs on intraperitoneal injection. Celler and Thallrimer (32) obtained a hemolytic streptococcus from gastric ulcers which, on intravenous injection, resulted in gastric lesions in a small percentage of rabbits (15%); however, when this was injected into a branch of the gastric artery, lesions were observed in 75% of the cases. Haden and Bohan (91) isolated a streptococcus from ulcer cases which, on intravenous injection into rabbits produced acute lesions in half the animals. Rosenow (176, 177, 178 179) has conducted extensive experiments along these lines. He has isolated strains of streptococci from foci of infection in tonsils, or from the ulcers themselves, with which, on intravenous injection, he has produced ulcers in animals. Ivy (110) has injected streptococci intravenously without being able to duplicate these results. Gerdine and Helmolz (79) isolated a streptococcus viridans from a duodenal ulcer of an infant which, on injection into rabbits and dogs, localized in the pyloric end of the stomach and there produced hemorrhage and ulcers. Haden (90) Nickel and Hufford (164), with others, have confirmed the results of Rosenow.

In an experiment on a group of dogs who had received extensive third degree burns, Hartman (99) reported that all the animals showed positive blood cultures, and 78% developed acute duodenal ulcers. In a group that were treated with penicillin, the incidence of duodenal ulcerations was reduced from 78% to 23%. This occurred in spite of the fact that penicillin inhibits the growth of only certain types of bacteria and, secondly, relatively small and infrequent daily doses of penicillin were used. According to Hartman, the experimental data would appear to indicate that the local and resulting systemic infection produced in these dogs with burns was of major etiological importance in the total pathogenesis of acute duodenal ulcers.

IV. MECHANICAL FACTORS

Among the methods, which have been studied extensively, that may cause or promote the chronicity of peptic ulcers have been those involving extensive mechanical trauma and chemical trauma. Such factors as foreign bodies, roughage, operative wounds, chemical irritants and the part played by the motor activities, i. e. those involving spasm, hypermotility and atonia have been given special emphasis.

1. Studies involving the motor activities; the pro-

pulsive force, or those activities causing stagnation. Bolton (25) produced acute ulcers in the stomach of cats by partially obstructing the pylorus. Friedman and Hamburger (73) partially obstructed the pylorus and injected silver nitrate in the submucosa to produce ulcerations. They found that it was in those cases in which the motility was most impaired and the hyperacidity most pronounced, that the chronicity of the ulcers was most pronounced. Slocomb (206) caused a partial obstruction of the duodenum of dogs and subsequently observed inflammatory changes and multiple ulcerations. Dragstedt (48) observed that interference with either gastric evacuation or regurgitation can produce stagnation, hyperacidity and, finally, peptic ulcer. Morton (155) produced duodenitis by encircling the pylorus with a constricting band of jejunal muscle. Shay et al. (200) observed the uniform production of gastric ulcerations following pyloric ligation. The lesions were most marked in the rumen and developed in seven to nine hours after ligation in starved rats. The authors observed that atropine, given subcutaneously in proper dosages, will inhibit gastric secretion in rats for many hours, and so prevent the gastric ulceration which follows ligation. In atropinized animals, the gastric installation of rat or human gastric juice as well as artificial acid-pepsin mixture readily produces the same type of ulceration which results from the routine experimental procedure of ligation.

Shay et al. (201) and others have used the Shay rat to evaluate various antacid and antipeptic agents. They have found that the greatest protection was afforded by colloidal aluminum hydroxide and sodium dodecyl sulfate. The combination of the two was better than either one singly. Next, in order of decreasing efficiency, were sodium aluminum silicate, magnesium oxide, dibasic aluminum amino-acetate in methocel, sodium bicarbonate and saline. The authors believe that the most important factor in the formation of ulcers in experimental rats was the actual peptic power ("peptic activity") of the unaltered gastric contents.

The Shay rat has been used to test various anti-ulcer factors in urine (169, 228), (see section on gastric acidity) which have been found to inhibit ulceration.

Driver and his co-workers (54, 55, 56, 57) (see section on gastric acidity) have studied the effect of hydrostatic pressure and various enzymes on the production of ulcers.

In Mann-Williamson dogs the effect of varying the propulsive force on the rate of formation and size of the ulcers has been studied by Mann and Bollman (135), McCann (142) and others. It has been pointed out (135) that the ulcers normally form one to two centimeters distal to the point of exit of the gastric contents and in the area where the material strikes first and with the greatest force. After the ulcer forms, if the jejunal segment leaving the stomach is made to continue in the same direction as the pylorus for several inches and then to bend sharply, the first ulcer, relieved from major mechanical trauma, heals; while the second ulcer will form at the intestinal bend. Restriction of the opening between the stomach and the intestine to produce a nozzle effect causes the ulcer to develop and perforate more rapidly. On the other hand, if the propulsive force of the stomach is decreased by surgically producing an hour-glass defect in the pre-pyloric region, the rate of formation is decreased.

2. Mechanical Trauma. While trauma to the digestive tract is not essential to the formation of ulcer, in many cases it appears to be a contributing factor and, occasionally, even a major factor in the development and maintenance of ulcer. It has been pointed out by a number of investigators that trauma resulting from the scraping of material along the gastric pathway tends to explain the incidence of ulcer in that region. Aschoff (4) has shown that ulcers experimentally produced by branding heal more slowly on the gastric pathway than in other parts of the stomach. The ulcers come into contact with gastric juice for a longer period of time and are injured more mechanically by the stomach contents. Morton (153, 154) excised pieces of mucosa from the lesser and greater curvatures of the stomach of dogs after a duodenal drainage operation, and found that the ulcers healed more slowly on the lesser curvature. He also transplanted jejunal patches with an intact circulation into different areas in the gastric wall of dogs on which duodenal drainage had been performed. Of four jejunal ulcerations in a series of thirteen cases, three developed in the lesser curvature and one elsewhere in the stomach, thus suggesting the greater activity of the destructive forces on the lesser curvature. In dogs on whom an Eck fistula had been made, Bollman and Mann (22) observed that in a considerable percentage of the dogs, acute perforated ulcers of the duodenum developed while they were fed coarse food containing much cellulose. When the coarse foods were replaced by a soft or liquid diet, the occurrence of ulcers decreased. These observations present control evidence that with a partial deficiency (qualitative or quantitative) of bile in the duodenum, the presence or absence of coarse cellulose food was an important factor in determining the frequency of the formation of ulcers in the duodenum. Mann and Bollman (134, 135) have observed that experimental ulcers produced by toxic factors were almost always in the pathway of the outflow of gastric contents, and they also emphasized the character of the food. In acute ulcers produced by excision or by injection of 5% silver nitrate solution, Ivy (107) found that manipulation — by massaging the lesions with bread crumbs, fingers, or cotton — delayed the healing of the ulcers two and three fold. Fauley and Ivy (63, 64) in further studies on the influence of diet, found that foods that contained much roughage delayed healing, while bland diets tended to have the opposite effect, which suggested their use in prevention and treatment of ulcers.

Ulcers were produced in prematurely weaned calves

by feeding coarse foods, as reported by Konjetzney and Puhl (125). McCann (142) pointed out that rough cellulose foods were not only factors in the production of ulcers, but might also cause perforations in post-operative jejunal ulcers.

V. Circulatory Factors

Virchow (229) first called attention to the possible relationship of local circulatory disturbances and peptic ulcer. He visualized the occurrence of hemorrhagic necrosis of the mucosa preceding ulceration, due to vascular ischemia — the result of vascular disease, particularly embolic occlusion. Cohnheim (37), reviewing the early literature, pointed out other hypotheses involving vascular phenomena, such as arterial spasm, impairment of venous outflow, mechanical hyperemia as a result of severe muscular contractions, and local hemorrhage, as a basis for ulceration.

Embolic experiments. A great variety of substances have been injected by various routes, with the production of acute ulcerations of the stomach. Panum (167) injected an emulsion of wax into the central end of the femoral artery of the dog, with the formation of acute gastric ulcerations and infarcts within a twenty-four hour period. Cohnheim (37) injected a lead chromate suspension into the gastric branches of the splenic artery, producing sharply circumscribed ulcers which healed in three weeks. Payr (170) and Grossi (84) produced acute ulcerations by means of retrograde emboli by injecting a bismuth subgallate solution into the gastric veins of dogs. Bolton (26) quoted various experimentors who reported inconsistent results with embolic experiments. Ivy (107, 108, 109) injected a number of substances into the gastro-epiploic vessels with variable results. Wilkie (229) injected solid particles of sterile oil into an omental vein with impaction in the smaller venous branches, resulting in gastric infarctions and acute ulcerations. At the same time, associated infarcts of the liver and spleen were observed.

The problem of acute ulceration following fractures to bones was investigated by Wangansteen and his co-workers (144, 145) (see section on histamine). A series of experiments was designed to test the three possible explanations proposed for the occurrence of ulcers following fractures or curettement; (1) histamine effect from the fracture site with the stimulation of gastric secretion, (2) fat embolism, (3) a combination of these two factors. To test the influence of fat embolism on ulcer production, fat was injected intravenously in rabbits, cats, dogs and guinea pigs. In rabbits, the injection of fat alone resulted in no ulcerations; but combined with histamine in wax injections, ulcerations were produced in all cases. This is significant in that rabbits are normally resistant to ulceration by histamine injections alone. Following single intravenous injections of fat, acute erosions or ulcerations were observed in a number of other animals. The fat was identified as plugging the arterioles in various tissues of the body. It was found that fat injected intravenously and fractures do not stimulate or augment gastric secretion in dogs with isolated gastric pouches.

In another series of experiments it was found (9) that partial obstruction to venous outflow increases the weight of the stomach of rabbits and dogs, with a resulting edema of the entire gastric wall, especially that of the mucosa and submucosa. Histamine ulcers were more readily induced in these animals than in normals.

Earlier experimentors had found that interference with the portal circulation alone has been associated with the development of ulcer. Mueller in 1860 (156) reported that the sudden occlusion of the portal vein was associated with the development of hemorrhages and acute erosions, located chiefly in the cardiac end of the stomach. In addition to other changes, Gundermann (89) observed hemorrhages and acute erosions in the stomach and duodenum following portal ligation; while Bollman and Mann (22) reported perforating duodenal ulcers in dogs with Eck fistulas fed coarse kernel foods. Baronofsky and Wangansteen (12) have observed that the administration of nitroglycerine in beeswax accelerated the formation of the histamine induced ulcer. The action of the nitroglycerine is attributed to its venous pooling property which coupled with normal arteriolar reflex contractile responses leads, after prolonged administration to resultant areas of impaired circulation in the mucous membrane of the esophagus, stomach and duodenum. As a result, the resistance of these areas to acid-peptic digestion is lowered and ulcers follow.

The injection of a number of drugs causing either spasm, local stasis or both — whether or not associated with the formation of ulcers — has been studied by a number of investigators. Westphal (227) injected large doses of pilocarpine subcutaneously, with and without physostigmine, into rabbits with the formation of acute erosions and ulcers. These he considered to be the result of spastic muscular contraction due to extreme vagal irritation. Viewing the exposed stomach of the rabbit, he observed long-continued spasmodically increased peristalsis, followed by cyanosis, pallor, and the appearance of whitish specks. These anemic foci he believed to be the starting points of the ulcers or erosions. His experiments with dogs, cats and guinea pigs were not so successful. Friedman (72) injected epinephrine repeatedly for a period of one to two weeks with the production of duodenal ulcerations. He noted that after the injection of pilocarpine, most of the lesions were in the stomach. Underhill and Freiheit (218), observing the exposed gastric mucosa of rabbits after injecting pilocarpine and epinephrine, concluded that the lesions depended on cyanosis of the stomach and localized areas of anemia, on which the gastric contents exerted a destructive action.

Dodds (44) has reported ulcerations in rabbits, cats, monkeys, guinea pigs, rats and mice following injections of an acetone picric acid extract of the posterior lobe of the pituitary. Nedzel (162, 163)

and Berg (19, 20) have reported gastric ulcerations following repeated intravenous injections of pitressin; and Metz and Lackey (148, 149, 150) have reported fundal lesions of the stomach following injections of pituitrin. It was observed that following the intravenous injection of posterior pituitary extract, a marked spasm of the mucosal vessels occurred, which was followed by bleeding in scattered areas, together with superficial erosions and edema. In addition, following a short period of atony, severe muscular contractions took place. It was concluded that these small ischemic or necrotic mucosal areas are digested by the gastric juices, and superficial ulcerations may occur. With repeated injections, the occurrence of ulcers in a certain proportion of the animals follows. Nedzel (163) reported seasonal variations in the frequency of ulceration, with a higher percentage occurring in winter and spring. The influence of sectioning the sympathetic and vagus nerves on the reaction to pitressin (betahypophamine) was noted by Berg (19, 20) (see neurogenic section).

The production of ulcer by chronic vaso-motor arterial spasm was studied in a series of experiments by Baronofsky and Wangansteen (11). Rabbits were given daily intramuscular injections of epinephrine and histamine in beeswax. In all the animals, ulcerations or erosions occurred, in contradistinction to the rabbits given histamine alone in which none were seen. In another series, epinephrine in beeswax alone produced both gastric and duodenal lesions. Repeated tests with adrenalin in aqueous form failed to reveal any definite stimulation of gastric secretion in Heidenheim and Pavlov pouch dogs. Similar lesions to the above were seen following injections of pitressin in beeswax. The depressant action of pitressin on gastric secretion was verified on Heidenheim and Pavlov pouch dogs. It was concluded that local spasm invoked by epinephrine and pitressin produce local areas of ischemia, which then become susceptible to the digestive action of the gastric juice.

In a study of ulcers produced experimentally by caffein, it was observed by Roth and Ivy (183) that in addition to the stimulation of acid and pepsin secretion by caffein, it produces hyperemia of the gastric mucosa, which is followed by cyanosis. It was postulated that the vascular stasis interferes with cellular nutrition and decreases the ability of the mucosa to resist injury by the acid pepsin.

METABOLIC AND ENDOCRINE FACTORS

Ulcerations of the gastric or duodenal mucosa have been associated with what have been called metabolic disturbances — so termed either for lack of more clearly defined criteria, or because the mechanism of action is unknown. This category embraces a wide variety of experimental procedures.

A number of chemical and physical agents have been injected directly into the stomach wall. Ivy (107), Friedman and Hamburger (73), Dragstedt and Vaughan (46, 53) and others have injected silver nitrate into the submucosa, with the formation of ulcers. Friedman and Hamburger, and Hughson (106) found that ulcers tended to become chronic when associated with delayed emptying of the stomach. Dragstedt and Vaughan (53) found that the lesions tended to become chronic when loops of non-absorbable suture material were imbedded in the gastric wall at the points of injury.

A great many substances have been administered systemically. Bolton (26) reviewed the work of some of the early investigators, who used various compounds of mercury and arsenious acid. Biologic products which produce gastric ulcerations have been studied extensively. Bolton (26) produced what he termed a gastrotoxic serum by injecting a suspension of gastric mucosa from a guinea pig into the peritoneal cavity of a rabbit. After repeated injections sufficient to build up an immunity in the rabbit, an injection of the rabbit's immune serum into the guinea pig intraperitoneally caused death associated with gastric ulcerations. Injection of this toxin directly into the gastric mucosa also caused ulceration. Latzel (127) injected sterilized gastric juice of guinea pigs subcutaneously into other animals, causing anaphylaxis and gastric ulcerations. Rosenau and Anderson (175) observed that diphtheria toxin, when injected subcutaneously into guinea pigs, caused hemorrhages and necrotic areas in the pyloric end of the gastric mucosa. These lesions were found in 66% of the animals. If the toxin was neutralized by antitoxin, no lesions appeared. In addition to ulcerations following the use of diphtheria toxin, an associated suprarenal congestion and pleural effusion were seen. Such effects were not obtained following the injection of tetanus toxin.

Shapiro and Ivy (197) reported the production of acute gastric ulcers in the fundus and pylorus of dogs and rabbits on the basis of local anaphylaxis to specific antigens. The sequence of observed events in the development of the acute lesions was: first, the development of passive hyperemia, edema, then central induration and necrosis.

Burns. Numerous investigators have studied the association of superficial burns, produced in a variety of ways, and the development of gastric and duodenal ulcerations. The explanation of the mode of origin of these peptic ulcers has not been clearly formulated. Four mechanisms have been postulated for the development: (1) toxic, (2) infection, (3) gastric stimulation, and (4) a combination of these factors. Necheles and Olson (161) studied gastric secretion in dogs with isolated gastrectomized stomachs, following torch burns to the hind legs of the animals. They found that such burns augmented gastric secretion if infusions of fluid were given simultaneously. On the other hand, contradictory results were reported by Hartman (98) who found that both the free hydrochloric acid and the total acidity were reduced following burns. In another series, Hartman (99) observed that where the incidence of infection was reduced, there was a marked reduction in the frequency of ulcer. Friesen and Wangansteen (76)

guinea pigs who had received daily implantations of caffein in a beeswax mixture. Studying the factors involved in the pathogenesis of caffein induced ulcers, Roth and Ivy (183, 184, 185) reported that in addition to stimulating acid and pepsin secretion by direct action on the parietal cells, caffein produces hyperemia of the gastric mucosa, which is followed by cyanosis. Speculating on the probable mechanism of ulcer formation in cats, the authors point to the proteolytic action of the acid pepsin secretion upon a gastric mucosa rendered more susceptible to the ulcerative process by the vascular and "toxic" cellular changes induced by caffein. In addition to these effects, there may or may not be a neurogenic factor, by virtue of the excitatory action of caffein upon the central nervous system.

In an interesting study by Giddings, Wynn and Haldi (80) the authors reported that caffein given by mouth or intramuscularly in amounts less than those which are fatal (75 mgm. per kilogram) produced no gastric lesions in cats. Caffein given in doses large enough to kill the animals may produce gastric erosions and ulcerations. They found ulcerations in three of four animals that died following the administration of toxic doses of caffein. In a series of 34 albino cats 75 mgm. of caffein per kilogram body weight, by stomach tube and over a period of from eight to 20 weeks, only three animals developed alterations on microscopic examination. They concluded, therefore, that coffee or caffein containing beverages play no part in the pathogenesis of peptic ulcers in humans.

Roth and Ivy (185) have taken issue with the findings of Giddings et al. They point out that toxicity depends not only on the absolute dose of a drug, but also on the route of administration and rate of absorption: and they contend that one is not justified in comparing directly the toxicity of doses when a drug is given in a rapidly absorbed and administered *route, to when the drug is given in a different* vehicle (beeswax) which slowly releases it for absorption.

VII. NUTRITIONAL FACTORS

Peptic ulcerations have resulted from the restriction of one or more dietary factors; and numerous experiments have been carried out to study the influence of starvation, deficiencies of proteins, vitamins, minerals, and unknown dietary factors, either singly or in various combinations.

Singer (1913) (205) observed epithelial hyperplasia and ulcerations of the forestomach in an experiment in which rats were fed bread and wood shavings. Hoelzel and DaCosta (101, 102) produced ulcerations in both the forestomach and glandular portion in rats and mice, when the animals were fed protein deficient diets and when they were fasted every other day. Matzner et al. (140, 141) ascribed the development of gastric lesions in rats fed low protein diets to the lack of protection from the proteolytic action of gastric juice. They found that more extensive lesions were produced when pepsin and hydrochloric acid were given together than when each was given alone, and felt that the high protein diets containing gelatin, casein and elastin afforded a measure of protection against the proteolytic action of gastric juice.

It was observed by Fauley and Ivy (64) that dogs operated upon develop lesions more readily on a restricted than on a full diet. Even such lesions as developed tended to heal if adequate diet was again furnished. Brunschwig and Rasmussen (27) observed that deprivation of food or marked reduction of adequate stock diets resulted in acute gastric hemorrhages which were not due to inadequate vitamin K. When a variety of inadequate diets were fed rats, resulting in malnutrition, ulcero-papillomas and papillomas developed in the stomach of the animals. The authors believe these lesions developed as a result of a certain degree of malnutrition, possibly the result of a deficiency of some as yet unidentified vitamin. Pure protein (casein) diets appeared to avoid the development of the lesions, as did pure brewer's yeast. Chen (34) observed that agar-agar and glucose afforded considerable protection against the formation of gastric lesions in starved rats, and questioned the importance of nutritional deficiency in the development of the lesions.

In a number of controlled experiments carried out by Sharpless (198), who used various deficiency diets and dietary supplements, it was shown that deficiency of cystine, riboflavin, pyridoxin, or choline induced hyperplasia and ulceration of the forestomach epithelium in rats. Sodium taurocholate or pepsin and hydrochloric acid increased the number and severity of the lesions in animals fed poor diets, but caused no macroscopic changes in rats fed stock diets. Limitation of intake of the stock diet caused no visible gastric lesions. In addition to lowering the resistance of the epithelium to irritation, the dietary deficiency may also provide an opportunity for prolonged contact between local chemical irritants and the epithelium. The action of the protective factors is interdependent so that a deficiency of one may prevent effective action by the others. It was postulated by the author that the mechanism of the formation of gastric lesions was the irritation of an abnormally sensitive epithelium by hair, hard food particles, pepsin and hydrochloric acid, or bile.

Li and Freeman (130) found that 47% of 32 dogs on protein deficient diets showed peptic ulcers when moribund. The minimum time required to develop ulcers was twelve weeks. The lesions were either single or multiple and were located either on the gastric or duodenal side of the pyloric sphincter. The protein deficient diets were practically free of protein except for that contained in yeast, which made up 5% of each diet. It was found that lower dietary fat content and the addition of bile salts seemed to favor ulcer formation. The incidence of ulcer, furthermore, could not be correlated with the survival period, hepatic dye clearance, serum phosphatase or liver lipids.

In the secreting portion of the rat's stomach, two types of mucosal lesions were observed by Berg (17). One is specific for the antrum and occurs when the diet is lacking in calcium; and the second is found exclusively in the fundus and results from inanition or starvation. Both lesions differ grossly and microscopically; however, bleeding is present in both lesions, being more profuse in the fundus than in the antrum. The fundic lesions are produced by short periods of starvation (two to four days) or by a thiamin deficient diet for one month. The antral lesions are produced by feeding a low calcium diet. By means of india ink injections, it was demonstrated that the differences in the bleeding tendency of the antral as compared to the fundal lesions were due to several factors: (1) greater vascularity of fundal mucosal defects of the same size (2) the subepithelial capillaries and collecting venules in the lining of the fundus are wider than those in the antrum, and (3) the sealing off of the ruptured vessels by thrombi is more apt to occur in the antral lesions due to the presence of an inflammatory reaction. The administration of ascorbic acid or vitamin K did not prevent bleeding from either lesion.

Vitamin A and associated deficiencies. Pappenheimer and Larimore (168) observed lesions in 55% of rats fed a rickets producing diet low in vitamin A. They felt that the lesions were the result of some intestinal factor and mechanical trauma. Wolbach and Howe (230) found that vitamin A was essential for the maintenance of normal epithelium in general; however, they found no forestomach changes in their vitamin A deficient animals. Extensive lesions in the forestomach were found by Fujimaki (77), which he attributed to vitamin A deficiency. Fredericia et al. (71) observed an 80% incidence of gastric ulcers in rats fed diets low in vitamin A and tocopherols. When they were fed the diet with the addition of butter fat (vitamin A) the incidence of ulcers was reduced to 18%; and it was therefore concluded that vitamin A deficiency was the chief factor in the formation of the lesions. Jensen (114) found ulcers of variable size located in the forestomach in vitamin A deficient rats. These ulcers were nearly always absent when tocopherols were added to the diet. The author believes, therefore, that tocopherols have a vitamin A sparing effect. Alcohol, it was observed, had an opposite effect.

As the result of a series of experiments, Harris et al. (97) observed that ulcers were induced in the forestomach of rats when (1) recovering from vitamin A deficiency, with the addition of 2, 30 or 300 units of vitamin A daily, (2) recovering from an essential fatty acid deficiency with 20 mgm. of linoleate daily, (3) recovering from vitamin B_6 deficiency with sub-optimal amounts of pyroxidine. The deficiencies of these three essentials did not in themselves result in lesions. The ulcers occurred only during the curative period in which the specific nutrient was fed. Alpha or gamma tocopherol fed daily to rats during the cure of the specific deficiency gave complete protection; but alpha-tocopherol-phosphate by injection was not effective. The amount of fat in the diet was related to the incidence of stomach ulcers in the vitamin A deficient experiments. Ten per cent fat provided good protection; five per cent resulted in moderately severe lesions which were preventable by tocopherol. Low fat diets gave very severe lesions not preventable by the level of tocopherol fed.

Vitamin B complex deficiencies. Dalldorf and Kellogg (42) and Sure and Thatcher (214) observed shallow ulcerations of the stomachs of rats on vitamin B_1 deficient diets. Findlay (67) observed gastric lesions with vitamin B_2 deficiency. Howes and Viviers (105) observed that the lesions occurred despite adequate protein intake if there was a vitamin B deficiency. The lesions occurred more readily in the young than in the old rats, and whole yeast afforded a relative protection. They concluded, therefore, that the whole vitamin B complex was necessary to maintain the normal forestomach epithelium.

It was demonstrated by Sharpless and Sabol (199) that choline and pyroxidine are necessary to help maintain normal epithelium in the forestomach of rats fed diets in which cystine and white flour furnish the only source of protein. It was found that calcium pantothenate does not improve such diets.

In a study on rats, Shay et al. (202) noted that in severe thiamin depletion, the volume of spontaneous gastric secretion was much greater than in corresponding controls; while the acidity, peptic power and total chloride concentration remained normal. This hypersecretion was shown to be a function of thiamin depletion alone. Gastric ulcers were observed in those rats on a calorically restricted, thiamin adequate diet as well as in thiamin depleted animals. The incidence, number and severity of the lesions were so much greater in the latter that it appeared to the authors that thiamin deficiency encourages peptic ulceration and that the mechanism responsible for this effect was the gastric hypersecretion which develops in the course of gastric depletion.

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Trends in Diagnosis, Etiology and Treatment of Duodenal Ulcer

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A REVIEW OF THE CONSTANTLY CHANGING subject of Peptic Ulcer reveals certain interesting and perhaps significant "Trends" in diagnosis, etiology and treatment.

DIAGNOSIS

In diagnosis (a fundamentally necessary prerequisite to treatment) there seems to be a trend *away from* "nonchalant guesses," "hunches," "snapshot" or "machine made" diagnoses and *toward* rational scientific decisions based upon careful and repeated observation and study of all pertinent (and at times seemingly impertinent) information gained by (a) history, (b) physical examination, (c) clinical and (d) X-ray laboratory findings.

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All of which presumes familiarity with and knowledge of a multitude of facts and fancies concerning the disease.

An understanding of *abnormal* functions calls for a knowledge of *normal* physiology, which is constantly increasing and far from simple.

Gastrointestinal function depends upon various mechanisms viz. (A) Nervous: The relationship between the cerebrospinal system and the constantly changing balance between the two divisions of the autonomic nervous system (the internal environment) and the variable external environment.

(B) Gastric, mechanical, chemical, and a possible hormone "Gastrin."

(C) Intestinal, hormonal.

With balance and synchronization between these various controls normal symptomless function occurs; without which, abnormal function produces "symptoms" which lead to treatment.

Many different conditions may be associated with similar "digestive symptoms" e. g. esophageal, gastric, duodenal ulcers, erosion or cancer, gastritis and duodenitis, hiatus hernia, diverticulae, gall bladder, liver, pancreatic and colon disease.

The facts that *hyper and hypochlorhydria* may produce similar distress, that the "pain, food, ease" sequence may not be diagnostically reliable, that gastrointestinal *hemorrhage* does not necessarily mean ulcer, that classical symptoms may exist without demonstrable ulcer, and that ulcer may exist without suggestive symptoms, create confusion and lead to diagnostic errors.

A familiarity with the results of both treated and untreated disease and a distinction between remissions and "cures," are necessary.

But a diagnosis of *so-called* peptic ulcer is *not enough*; its location, gastric, duodenal or elsewhere is called for.

But, in turn, a diagnosis of gastric ulcer is not enough; a distinction between *malignant and non-malignant* is imperative. It is difficult and at times may be impossible, before microscopic examination.

The *fact* that an undetermined *per cent of gastric (in contra distinction to duodenal) ulcers are, or* become, malignant. (1) justifies Dr. Allen's conclusion that "Gastric ulcer is primarily a surgical lesion" (2).

Other necessary diagnostic details are: Is the ulcer acute, chronic, growing healing, simple, complicated, penetrating, bleeding, *obstructing*, "intractable," single or multiple?

Not only *correct* but complete diagnosis is called for. Coincidental disease must be recognized.

(a) The "sheet anchor" *of* diagnosis is the "history," story *of the* chief complaint, i. e. the endless variety of pain, tenderness, "gas," so-called "dyspepsia," "indigestion" etc. etc.

These *subjective* symptoms are "Nature's" attempt to speak through the patient to the physician. The language is often difficult for the patient to *express*, and also for the physician to *understand*. Therefore the history must be secured and recorded, not by a stenographer or clinical clerk, but by the physician himself, with the check and double check, by judicious cross questioning.

The stomach has been called the "sounding board" for disturbances in other organs of the body.

It is well known that extra-gastric disease, such as *acute* heart, lung, kidney or cerebrospinal lesions *may, reflexly, produce acute* abdominal *symptoms*; but the fact that *chronic* disease of these same organs *may produce chronic* abdominal symptoms that may, *at times*, be confused with peptic ulcer, has not been equally emphasized.

A reversed "*sounding board*" reaction in which gastric lesions cause remote symptoms and asymptomatic peptic ulcer, are recently being recognized.

All of this *necessitates consideration*, not only of the stomach and duodenum, but of the entire gastrointestinal tract with its offshoots and the many other organs and systems of the body, i. e. "the patient as a whole" with his reaction to the external environment.

(b) *Physical examination* is of comparatively little aid. Localized *tenderness* and *rigidity* or muscle spasm will be helpful.

(c) Routine clinical laboratory findings are important. The *presence or absence* of Hydrochloric acid after histamine is valuable. Achlorhydria suggests cancer, but the *presence* of hydrochloric acid *does not exclude malignancy*.

(d) X-ray barium examination, when included with the history, case records, and laboratory data, is always valuable and often conclusive. But a picture *of a shadow when considered alone*, may be misleading. Fluoroscopy is essential and of more value than films, which *should be chiefly* for record and *comparison*. Because of possible reflex spasm, repeated examinations after antispasmodics may be indicated. The meal should be observed through the *entire gastrointestinal tract and, in obscure cases*, a "check-up" by barium enema is indicated.

Cholecystography should be routine in so-called "gastrointestinal examinations."

The term "X-ray diagnosis" might well be abandoned and the term "X-ray findings" be substituted.

Realizing the *necessity* of early diagnosis if results in cancer are to improve St. John, Swenson and Harvey (3) employed mass fluoroscopy after barium meals as a method of "screening" similar to mass chest films in detecting pulmonary tuberculosis, but it was considered impracticable.

The suggestion of such "mass fluoroscopy" in cases of achylia seems worthwhile.

The trend seems to be, in obscure cases, to collect, organize, analyze and study all available information in an attempt to improve diagnosis.

ETIOLOGY

A rational concept of *cause* is a necessary preliminary to successful treatment. The cause of peptic ulcer is evidently not single, but multiple, differing with the individual and upon circumstances. Their mere enumeration, neurogenic, vascular, inflammatory, toxic, mechanical, traumatic, dietary deficiency, endocrine, allergic, constitutional, hereditary etc. etc. speaks against a single cause.

The occurrence of peptic ulcer in infancy; the

infrequency of this disease among patients in mental hospitals and prisons; and the rarity of peptic ulcer after the operation of sympathectomy, seem to invalidate the neurogenic basis. The failure to discover peptic ulcer after prolonged irritation of gastric foreign bodies, seems to discredit the traumatic theory. "Focal infection" has failed to explain many cases. The frequent occurrence of peptic ulcer in the "family history" and four recorded instances in twins (4) emphasize the importance of constitutional hereditary factor.

As Allen Gregg (5) says, "We must further expand our thinking from simple and unique causative to include knowledge of the laws of pure chance of multiple causation and of correlations."

The words "dyscrasia," idiosyncracy," "diathesis" and "constitutional inadequacy" have been used in attempts to explain some basic etiologic factor. A late term by Roth (6) is "the commonly associated psychomatic substrate."

If, as is generally accepted to-day, peptic ulcer is a general disease with a local lesion, or as Kuntz (7) says, "The ulcer is but a symptom of a more fundamental disorder," the question, what is this "general disease" or "fundamental disorder," naturally calls for an answer.

As in most scientific problems, an answer merely prompts another question. Why the hypersecretion or the diminished resistance?

The question is not only, what causes the peptic ulcer, but what causes the *chronicity,* what prevents the ulcer from healing?

But the generally accepted basic fundamental explanation concerns an *imbalance* between an aggressive (Hydrochloric-pepsin) and a defensive (alkaline-mucosal) factor, with a resultant hyper or hypochlorhydria.

The importance of hyperchlorhydria is emphasized by the fact that without hydrochloric acid there is no "peptic" ulcer, though gastritis, erosion and other types of ulceration, may occur. (Hyperchlorhydria has been considered by some to be a result rather than a cause of peptic ulcer).

The locations of peptic ulcer, in alkaline secreting surfaces adjacent to hydrochloric acid secreting surfaces such as the lower esophagus, the distal stomach and duodenum, the jejunum after gastroenterostomy, and the terminal ileum adjacent to Meckel's diverticulum with heteroplastic acid secreting cells, all stress hyperchlorhydria as an important etiologic factor (8).

In the current literature one may note a *trend* toward de-emphasis of hyperchlorhydria and an emphasis upon an absence of an anti-ulcer factor. Heuer (9) suggests that the cause may be other than increased hydrochloric acid secretion.

Yasinovskiy (10) states that, "There is no definite parallelism between the clinical course of peptic ulcer and acidity of the gastric contents."

Bachrach, Ivy et al (11) in discussing the cause of peptic ulcer consider "The resistance of the gastrointestinal tract to the digestive action of its own secretions."

Whether Hydrochloric acid is or is not a significant etiologic factor, it is important because of its repercussions upon treatment and prevention.

Babkin (12) and others have emphasized the importance of pepsin but as this ferment is active only in an acid medium, it seems of secondary importance.

TREATMENT

The real objective of treatment is not only an immediate remission, but the prevention of a remote recurrence.

Treatment is at present generally based upon hyperchlorhydria as a chief cause and therefore aims to reduce secretion of hydrochloric acid or the Ph of gastric contents.

As has been shown above, the cause of peptic ulcer is not single, but multiple, it should logically follow that treatment must be multiple and not single.

Treatment has been divided into non-operative (or medical management) and surgical.

Because of a potential malignancy, gastric ulcers must be considered as "essentially surgical until proven otherwise." And gastric resection, rather than local excision, is indicated.

Duodenal ulcer, which is now recognized as a "general disease with a local lesion," is treated by medical management, with surgery indicated not for ulcer but for the usual complications, viz. hemorrhage, stenosis, perforation or intractability.

Acute hemorrhage is generally treated medically, but if due to erosion of a sclerotic artery, surgical measures are imperative. Failure, at times, to find the source of bleeding, at laparotomy, or even at autopsy, tends to discourage surgical treatment.

Stenosis is often due to edema, hypoproteinemia, and will usually subside after bed rest, decompression and suitable physio-medico management. If due to scar tissue, surgical measures are necessary.

Perforation calls for immediate laparotomy and closure of the perforation. Attempts at "cure" of the ulcer are usually postponed to a subsequent period. Under certain circumstances tubal decompression and non-operative treatment has been reported by Taylor (13).

The "intractable" case, as the name implies, does not respond satisfactorily to proper treatment. Allen (2) says that "Intractable ulcer may be an intractable patient."

NON-OPERATIVE TREATMENT

A trend to accept the importance of *non-operative management* is shown in the fact, often overlooked, that surgical treatment of any type is but an incident, often a most important incident, between pre- and post-operative management, that calls for practically constant adjustment and supervision.

Non-operative management includes many different methods and details often conflicting and constantly changing, but the general objective is to reduce hydrochloric acid (aggressive factor) and to increase the mucous (defensive factor), chiefly by *diet* with extremes of Lenharts, of Sippy and of Meulengrath and a multitude of variations with vitamins, hormones or amino acids; By *frequent feedings*, not only for nutrishment, but also to dilute the aggressive hydrochloric acid and to provide contents, instead of gastric mucosa, to be acted upon by the gastric secretion; By *physical bed rest*, to among other things, diminish local stasis; and by *psychic rest* by change of environment or by explanation of the rationale of the treatment, and by anti-spasmodics, antivagal and pro sympathetic drugs.

Alkalies and antacids, *because of* indirect "kick-back" secondary acid stimulating actions, have been largely replaced by aluminum preparations, adsorbents, fats and other antisecretagogues. Protein administration is becoming an important detail in the treatment, resins are now recommended not only for hemorrhage but also as a new antacid. X-ray therapy has not been successful.

Future of non-operative management looks hopefully to the isolation of a clinically applicable antisecretagogue viz. Enterogastrone by Ivy (14), Urogastrone, Sandweiss (15) or by an anti-ulcer substance (not an antisecretagogue) Antheloin. Results as yet, are undetermined.

Satisfactory clinical results after Enterogastrone in 40 of 58 cases are reported by Ivy (14) and Hubacher of Switzerland (16) reports 43 of 54 cases. Saltzstein, Sandweiss et al. (17) reported favorable results upon Mann-Williamson dogs.

Insulin in Diabetes, Liver Extract and Folic acid in Pernicious anemia, "Thiouracil" or its newer developments in non-operative treatment of hyperthyroidism, all give hope for a comparable treatment in duodenal ulcer.

Further study in physiology of psychosomatic disorders, of blood pressure, of peripheral vascular disease, of causalgia and of metabolism with special reference to balance between extra cellular sodium and intracellular potassium, and the question of membrane and capillary permeability, may reveal newer methods of treatment. Salt restriction is being employed in management of various diseases and theoretically it would seem to have a place in efforts to reduce hydrochloric acid secretion. Substitution of bromide for chloride seems to have been beneficial at times.

The discovery of the why and wherefore of the achlorhydria of pernicious anemia, cancer of the stomach or gastritis, may influence future treatment.

Immediate results of non-operative treatment are usually satisfactory.

Remote results are not so good. A late report by Heuer (9) states, "These results are not static, but will become less favorable as time goes on." In 732 cases hospitalized (not previously operated upon) results were unsatisfactory in 81. (To every case hospitalized five or six cases were treated in out patient department). The remaining 651 with 10 year follow-up had satisfactory results in 61.1%.

"In this series then," Dr. Heuer continues, "the mortality rate, directly from ulcer treated medically is 3.5%, a mortality which in our experience approaches closely that of gastroenterostomy or gastric resection."

Raimondi and Collen (18) noted 90% relief in acute ulcer, but with recurrence in two years in 83%.

From Copenhagen, Kraup (19) noted poor results in 28% in 665 cases 1931 to 1938.

Ivy (14) collected 938 cases with recurrence in two years in 87%.

Kahrs and Schrumpf, Norway (20) report 21% satisfactory results after three to eight years in 172 cases treated non operatively.

Althausen (21) discusses "Medical Treatment versus Prevention of Peptic ulcer."

OPERATIVE TREATMENT

Operative treatment, based upon the hyperchlorhydria etiology, may be divided into *indirect* (1) Excision of the ulcer, (2) Pyloroplasty, (3) Gastroenterostomy and (4) Antrumectomy: and *direct* resections of the proximal, acid secreting, stomach.

Indirect:

(1) Routine removal of the ulcer is strongly urged by Lewisohn (22). If the ulcer is allowed to remain, he suggests the term "Palliative" resection.

Mage (23) says, "While it is assumed that radical resection of the ulcer is the best available operation at present, the impression is gained that it leaves much to be desired."

Satisfactory results have followed treatment in which the ulcer was not removed, e. g. in all non-operative management, and in many gastroenterostomies and resections in which the ulcer was "non-resectable."

Excision of the ulcer, if convenient, as a supplement to resection, in an attempt to remove or minimize a cause, seems rational and advisable, but if the cause is removed, excision of the ulcer, as in varicose ulcer of the leg, may not be necessary. By itself it is like locking the door after the horse has been stolen. There is little reason to think the scar

tissue after excision of ulcer would be more resistant to the factor causing ulcer than was the original mucosa.

(2) Pyloroplastics, after a fair trial, have been abandoned.

(3) Gastroenterostomy alone, has passed through protracted periods of general acceptance and rejection, but at present (because of return of symptoms and frequent jejunal-stomal-ulcer) is practically limited to *organic* pyloric obstruction (in D. U.) and in inoperable ca. of the stomach. Neutralization of gastric contents by duodenal regurgitation is probably its chief therapeutic advantage in nonobstructive cases.

(4) Antrumectomy with sacrifice of the pylorus and the resulting substitution of an artificial, nonphysiologic, non-sphincteric gastro-intestinal communication calls for many physiologic readjustments and adaptations in the digestive processes that probably cause symptoms and should, if possible, be avoided. Nature's post-operative attempt at sphincter action at the stoma may sometimes be seen at fluoroscopy. Kennedy et al. (24).

Disturbance with, or destruction of, other sphincters, e. g. pharyngeal, esophageal, biliary or urinary, disturb normal function and produce distressing clinical symptoms. The consequences of loss of control of the anal sphincter are very evident and deplorable. Loss of control of the pyloric sphincter may be followed by serious digestive disturbances, despite the fact that the results are not as apparent.

The opposite condition, pylorospasm or stenosis, certainly causes recognized signs and symptoms.

In the current literature one finds emphasis upon the alleged importance of antrumectomy "radical resection of all antral tissue," in the successful surgical treatment of peptic ulcer. This is based essentially upon the theory of Edkins (25) i. e. that the antral mucosa secretes an alleged hormone "Gastrin" that is carried to the fundus and stimulates the secretion of Hydrochloric acid. This theory was presented in 1906 and has not been *proven* by physiologists or clinicians.

In 1941 (26) I discussed this theory and its relation to Hydrochloric acid secretion.

The question of the importance of the antral secretion is continued as may be seen by recent articles by Uvnas (27) in Scandinavia and Schilling and Pearse in America (28).

It is of interest to note that a fortuitous clinical application of the then unknown Edkin's Theory was previously carried out in the distal resection of the so-called "ulcer bearing area" of the Rodman operation (29) which was soon discarded.

Among the objections to antrumectomy alone, or with more proximal resection, one may mention that the antrum takes an active and important part in the physiologic antro-pyloro-duodeno-muscular mechanism that controls the pylorus and which influences gastric tonicity, mobility, retention, evacuation, secretion and absorption. Other unfavorable results are loss of alkaline antral secretion, chiefly mucous, one of Nature's buffers, which may also contain Castle's "Intrinsic Factor."

Granting, for argument's sake, the antral development of "Gastrin," an hormone (not histamine, but a histamine-like substance) its obliteration by antral resection would reduce secretion by but a *fraction*, as at least three other important stimuli remain intact, viz. nervous (psychic, vagal), gastric (mechanical) and hormones formed in the duodenum or upper jejunum. That the duodenal glands of Brunner might "carry on" for the removed antral glands, is strongly suggested by their structural similarity. Their difference seems to be chiefly in their anatomic (or histologic) relationship to the submucosa,

Recently under the title, "Histamine and Gastric Secretion in Relation to Anti-Histamine Drugs," Ivy (30) states, "Although the final word is yet to be spoken, the weight of evidence now available indicates that histamine is not gastrin and that histamine may be released by the gastric and *intestinal* mucosa only when the mucosa is irritated mechanically or chemically."

The importance of this distinction is that, *if* "Gastrin" is not an entity, elimination of the antral secretion could be readily replaced by histamine originating in the intestine or elsewhere. Especially so when one remembers the propensity of "Dame Nature" to establish compensatory mechanisms for loss of many functions.

The removal of the antrum alone has not been satisfactory so there has been gradual extension a "shift to the left" with direct minimization of more and more of the fundal mucous membrane capable of secreting hydrochloric acid.

Before discussing direct treatment, it will be helpful to recognize the fundamental fact that the stomach is a double organ (1) a proximal fundus which is the dilated greater curvature and acts as a reservoir for mixing food with its special acid, pepsin and other secretions and (2) a distal antrum, funnel shaped, secretes alkaline mucous and a possible hormone and which with the lesser curvature (the "Magenstrasse") serves for transportation and with the pyloric sphincter controls emptying.

Such a division is substantiated by a study of comparative anatomy in which many lower animals are found to have a double stomach and also by a study of human embryology which suggests that the proximal stomach is a modified special organ.

The primitive straight foregut is seen to develop various organs by *eversion* (outward bulging) of certain areas, e. g. salivary glands, liver, pancreas which connect with the lumen by means of a *narrow duct* and also the spleen and thyroid which are *without a duct*. The proximal dorsal border of this straight tube

enlarges to the *left* and becomes the greater curvature and the fundus, which communicate with the lumen by a *broad opening*, while the distal ventral border is thrust to the right to become the pylorus, antrum and lesser curvature.

The foetal development of the *intestinal* tract with its complicated retraction, ascent, migration, rotation and descent of the ileocecal junction have been well described, (31) but the less striking evolutionary changes in the primitive foregut, the stomach, have not been equally emphasized.

Histologically different types of glands are to be found, in the fundus acid secreting, and in the antrum alkaline secreting.

The fundal cells rarely extend for a short distance into the lower esophagus, but the antral cells constantly extend into the upper duodenum, as Brunner's glands, which differ chiefly in their relationship to the submucosa.

An appreciation of this physiological difference between the proximal and distal stomach might be well worth consideration in surgical treatment of peptic ulcer.

DIRECT TREATMENT

The next step in the transition of surgical treatment of duodenal ulcer was aimed at direct reduction of hydrochloric acid secretion, by removal of more and more acid secreting fundal wall. (The favorable influence of incidental rest and neutralization following the associated gastroenterostomy remained, of course, the same).

Removal of more and more fundal acid secreting gastric wall, in a "shift to the left," through partial to subtotal gastrectomy, was followed by increasingly favorable results.

But the present popular "subtotal resection" is not entirely satisfactory, which may be seen in a trend of increasingly frequent reports of so-called post gastrectomy or "Dumping" syndrome (32).

This syndrome may include intermittent diarrhea, weight loss, a possible primary anemia, post prandial epigastric distress, distention, nausea, vertigo, perspiration, palpitation, asthenia, quantitative dyspepsia and gastro-colic reflex, due in some cases to an hypoglycemia, or to hypoproteinemia.

Post operative stomal or jejunal ulcers do occur despite extensive resections, the susceptible area of the duodenum seems at times, to be transferred to a more susceptible area in the jejunum.

The dissatisfaction may be seen more definitely in the continued efforts to develop newer treatments, non-operative, mentioned above and in surgery by what seems to be a trend away from the presumably accepted extensive mutilating, unphysiologic, subtotal gastrectomy and toward various types of less extensive, more conservative surgical procedures.

For example: Heuer (9) of New York Hospital suggests a return to gastroenterostomy with a less radical resection, and claims that cure depends not so much upon diminished acid secretion as upon neutralization.

Andrus, Lord and Steffko (33) transplanted a segment of alkaline secreting jejunum into the gastric wall and reported satisfactory clinical results, which were not confirmed by others.

Somervell (34) reported satisfactory results after ligating the large gastric blood vessels, but a coincidental gastroenterostomy in many cases confused the attempt to evaluate the results.

(The author in 1929 carried out mass ligation and removal of the fundal mucosa, experimentally, on dogs, but with unsatisfactory results).

The procedure has not been accepted. Leven (35).

Dragstedt (36) has recommended *complete* vagotomy with the objective of removing the cephalic or psychic stimulant to the secretion of hydrochloric acid.

This procedure has attracted much publicity and has been given an extensive clinical trial by himself and by many others.

The subject has been discussed in a voluminous literature which will not be reviewed here. (Alvarez and many others (37).

The immediate results are indeed dramatically favorable, but frequent coincidental gastroenterostomy or resections confuse the issue. Similar dramatic results have followed various other types of surgical treatment, such as: removal of the "Noxious antral remnant" or partial fundusectomy, newer non-operative dietary management; and in cases not treated at all, or by change of environment such as a vacation, ocean voyage, or sojurn in the north woods.

With elapse of time, reports of recurrences are increasing.

Subdiaphragmatic vagotomy is not new, it had been carried out with unsatisfactory results because of failure to include *all* fibers of the nerves. Dragstedt previously divided the nerves above the diaphragm, but now divides them sub-diaphragmatically, after the lower esophagus is delivered into the abdominal cavity.

Complete vagus division is technically difficult because of the varied ramifications and distribution and branching of the nerves of the esophageal plexus.

The Insulin test of Hollander (38) is useful in determining the completeness of the vagotomy.

Dragstedt (36) says "Many physicians have called attention to the high incidence of ulcers in individuals whose occupations subject them to continuous mental strain, worry and anxiety and the tendency for exa-

cerbations to occur during periods of emotional stress."

This observation is undoubtedly true and has been confirmed by Wolf and Wolff (39).

If "mental tension" may be described as (Berliner et al. (40), "---- a persistent emotional change which is always of an unpleasant quality, invariably distressing and sometimes intolerable to the patient; its presence is shown by irritability, rage, fear or other forms of emotional excitation, insomnia, restlessness aggressiveness, destructiveness or impulsive behaviour" it would seem fair to draw attention to the equally true observation that inmates of mental hospitals are infrequently afflicted with peptic ulcer.

At Winnebago State Hospital, where I have been consultant for many years, cases of P. U. are few and far between.

Burden (41) has discussed the occurrence of P. U. in prison inmates.

Cushing's (42) re-emphasis of Rokinansky's neurogenic theory of etiology and report of cases, does not seem to have seriously interferred with the progress of brain surgery.

The question of constant night secretion has not been settled (43).

Dragstedt says, "The central nervous disturbance causes ulcer by producing hypertonus in the secretory and motor fibers in the vagus nerve."

One might well ask what produces this hypertonus?

This is answered in his next paragraph. He states, "Perhaps this may lie in adjusting the individual to his work and environment so that these tensions do not arise."

Comparison of results after division of the sacral and cranial outflow of the parasympathetic nervous system might be instructive.

The fact that relief of dysmenorrhea has not been permanent following operation upon the Nervi Erigentes (the sacral division of the parasympathetic nervous system) suggests the possibility that the results of division of the cerebral component of the same system may be equally transitory.

Theoretically if vagotomy *cures,* or improves, peptic ulcer, then sympathectomy should *cause* or aggravate, this same disease. The antagonistic or perhaps compensatory action of the two divisions of this autonomic system are not clearly defined.

Follow-up reports on many sympathectomies fail to show any appreciable number of resultant peptic ulcers.

But even granting the destruction of the psychic stimuli to secretion of Hydrochloric acid, three other stimuli remain in action and may reasonably be relied upon to compensate for the loss of the vagal stimulation.

This would be similar to the compensatory action after removal of the antrum, at the distal, or of the fundus, at the proximal end of the stomach.

Nature is most prodigal in establishing compensatory mechanisms after loss of many important functions as in vascular "collateral circulation." It would therefore seem reasonable to anticipate that other structures might "carry on" for the resected vagus nerve.

The fact that Histamine stimulation of hydrochloric acid continues after operation would tend to minimize the importance of vagotomy.

Motor disturbances are apparent for four or five post-operative days. If such motor effects are but transitory, it would seem logical to anticipate similar short secretory results.

The definite physiologic *gastric* changes that follow vagotomy suggest the possibility of similar functional changes in the distal gastrointestinal tract.

Despite these theoretical objections, complete vagotomy may prove to be a valuable detail in the management of certain types of peptic ulcer.

The enthusiasm in favor of vagotomy seems to be subsiding as the unsatisfactory results increase with longer follow-ups.

Recent articles report or admit failure in gastro and duodenal ulcer, but advocate without explanation, the procedure for jejunal or stomal ulcer.

This review of the development of the surgical treatment of duodenal ulcer reveals two important facts (1) gastrojejunostomy alone or with distal (alkaline secreting) resection was not satisfactory (2) that results improved "pari-passu" with removal of more of the proximal (acid secreting) stomach (that is subtotal resection).

These two facts coupled with the increasing occurrence of so-called "Post-gastrectomy syndrome" prompt the following question. Can the advantages of the proximal resection be secured without the disadvantages (anatomic and physiologic) of distal resection?

In an attempt to diminish deformity and to minimize surface of stomach capable of secreting HCl by more conservative measures, the writer (44) in 1928 recommended proximal resection "partial fundusectomy."

Such resection reduces the acid secreting mucous surface by direct minimization (instead of indirect measures) and preserves (instead of sacrifices) the antrum with its important alkaline secretion (despite Edkin's Gastrin theory) and the normal motor continuity of the g. i. tract, with its sphincter mechanism.

This procedure has phylogenetic, embryologic, anatomic and physiologic evidence to support its rationale and may be likened to partial thyroidectomy or pancreatectomy.

(With *organic* pyloric obstruction, pyloroplasty or gastroenterostomy will be a necessary supplemental procedure).

Such an operation does not permanently alter normal anatomic or physiologic relationships (45) and if recurrence occurs, subsequent surgery may be simpler and safer than after more mutilating measures.

In March 1948 (46) the writer reported clinical results of 25 such cases, as follows:

Partial Fundusectomy for Intractable non-obstructing duodenal ulcer.

19		6
Satisfactory		Unsatisfactory
Over 10 years	6	4 refused second operation
Over 5 years	5	3 second operations
Under 5 years	7	2 hospital deaths
After second operation	1	(1 satisfactory after 4 years)

The frequent recurrence of ulcer, despite removal of fundal wall with, or without, distal resection, the questionable results of psychotherapy and the recurrence of hyperchlorhydria without coincidental peptic ulcer, have given rise to more serious consideration of the concept of an humoral, (hormonal) endocrine or anti-ulcer factor in the etiology of peptic ulcer.

Ivy, Cummings and Grossman (47) have instituted studies of balance, or imbalance, between the systemic and the gastric content Ph.

In attempts to evaluate treatment one finds more and more attention given to the fact that this disease is characterized by spontaneous, unexplained remissions and recurrences with consequent less "Post hoc ergo propter hoc" reasoning and longer "follow-ups" before speaking of "Cures."

SUMMARY

In Diagnosis, the "trend" seems to be *away from* "hunches," "snapshot" impressions, or machine-made diagnoses and *toward* more correct and complete scientific diagnosis; based upon studies of the history, repeated observations and various laboratory analyses, with consideration of the entire person and the environment.

In Etiology, the "trend" seems to be *away from* a *single cause* and *more toward* many different malfunctions with de-emphasis of the acid factor and more attention given to an intangible anti-ulcer mechanism.

In Treatment the advisability of a differentiation between gastric and duodenal ulcer is being recognized.

In gastric ulcer, the "trend" seems to be *away from* non-operative management and *toward* more extensive surgical resections.

In duodenal ulcer the "trend" seems to be *away from* surgical treatment and *toward* non-operative management.

Surgical treatment (when indicated by complications) trends *away from* extensive mutilating resections, and *toward* more conservative anatomical and physiologic operations.

Surgery is becoming recognized as but an incident, a most important incident, between pre- and post-operative medical management which must be continued indefinitely.

With favorable results depending upon cooperation between the patient and the physician.

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NUTRITION

Soil, Food and Health *

By
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THE TITLE OF THIS ADDRESS may seem out of order for a therapeutic society. Upon reflection, however, we are aware that soil, plants and animals have provided witch doctors and medicine men with devil-chasing potions, magic brews and more recently physicians with their tinctures, fluid extracts, elixirs, glandular extracts, vitamins and countless other articles listed in the pharmaceutical catalogues for the amelioration or relief of human suffering.

Fertile soils, healthy plants and healthy animals constitute our most potent therapeutic apparatus for the maintenance of health and the prevention of most diseases afflicting the human organism. This is a

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fact which most physicians and scientists have been tardy to appreciate or recognize. Man's health depends more upon healthy soils, plants and animals than upon miracle drugs and "Fountain of Youth" serums. As therapists, our concern should be more with the prevention of physiobiologic wreckage than with the end results of improper nutrition and improvident living. We should realize that public health is no longer a matter of Federal, State and Municipal appropriations of huge sums of money for therapeutic facilities available to everyone. Health can be purchased in a well organized food culture — it cannot be purchased as a commodity in hospitals, clinics or custodial institutions. In the last analysis physicians, hospitals and other medical service institutions are in the business of treating sickness. Until we overcome our distorted therapeutic habituations and cease to think of health in terms of remedial measures for sick people, our health programs shall be farcical.

For centuries we physicians have been breathing the miasmic odor of biologic decay in the dismal swamp of pathology. We are more proficient in the detection of biologic decay than we are in the recognition of biologic health. In other words we are like the institutional psychiatrist who rarely contacts a normal person and when he does, he at once attempts to distort normality into abnormality. When we emancipate our minds from the therapeutic aspects of pathology, enlarge our etiologic horizon beyond the boundaries of Pasteurian pastures populated with microorganisms which we have blamed for most of mankind's miseries and become concerned with where good or bad food and animals are grown, then we shall begin to realize that Nature has provided us with an ecologic pattern that is self-sufficient for the survival of all species.

Unfortunately, with the development of what we call brains, we have progressively disturbed, distorted and frustrated the ecologic provisions of Nature and we are now paying for it in terms of more hospitals, clinics, custodian institutions, penal institutions and a misdirected social apparatus which baffles our best minds in respect to the future of mankind.

II

Soil is the product of rock weathering, soil material accumulation and a "plant-climate" environment which provides and incorporates organic materials and biologic life in the surface soils. The soil must teem with chemical and biologic activity. It is from this kind of a soil that new plant life emerges to provide us with the many organic substances necessary for animal life.

To really appreciate the genetic origin and development of soil one must think of its accruing in stages or steps. Of primary importance is the metamorphosis of geological rock materials into *soil materials — not soils.* The soil material is exposed to and endures many different kinds of environment which are climatic (temperature, moisture, drainage) as well as the biologic activity of microorganisms, earthworms, insects and fungi. After these factors have contributed their effects, then, and only then, do we have soil. Soils vary greatly in their regional characteristics even though the parent geological material may be almost identical. For an exhaustive discussion of this subject one should review Dr. Marlatt's "Atlas of American Agriculture — Part III, Soils of the United States," or Milton Whitney's "Soils and Civilization."

Nutritionists and soil chemists agree that proper nutrition and the role that it plays in the maintenance of good health involves twelve factors:

1. The ecologic equilibrium of the fauna and flora of the soil.
2. Fertility of the soil.
3. The vigor of the germ plasm of the seed.
4. Climatic factors — temperature, moisture, sunshine.
5. The proper culture of the flora and fauna which supply man with food.
6. The harvesting and storage of food.
7. The handling of food during transportation and distribution.
8. The methods of processing through which food has gone — milling, canning, brining, salting, dehydration, freezing, sun-drying, curing and smoking, sulfuring, dyeing, etc.
9. The intelligent selection of food at the market.
10. The proper preparation of food either for immediate consumption in the raw state or for cooking.
11. Proper methods for cooking different kinds of food.
12. The proper care of left over food to be used at subsequent meals.

Many of our most fertile areas are geologic happenstances. Other factors are involved, and I shall review some of the most important of these.

Fertile soils are live soils, populated by countless numbers of bacteria, fungi, molds, yeasts earthworms and insects. Bacteria, fungi, molds and yeasts are important because they manufacture and excrete enzymes which control the digestive processes of the soil. The more fertile the soil, the more biologic life it contains. At the Rothamstead Agricultural Station in England bacterial counts per gram of soil decreased from 28,860,000 on soils fertilized with farmyard manure to 15,100,000 on soils treated with artificial fertilizers. It was noted that poison sprays caused a serious reduction in the soil's micro-flora.

If left alone, Nature supplies a wide range of fertilizer materials at no expense — we have only to take advantage of the natural cycle of growth, decay and return. In fertile soils it is estimated that the number of bacteria in an acre may weigh as high as

600 pounds. When they die, their bodies undergo decay — being split up by enzymes and other forms of microbial life into simple elements which are returned to the soil. These tiny organisms, because of their prodigious growth under favorable circumstances, are effective helpers in maintaining soil fertility.

The lowly earthworm, with a life span of not more than a year or two, was considered fish-bait until Darwin studied its function in soil. It is estimated that the weight of dead earthworms in fertile soils may amount to over 500 pounds per acre. What a fertile source of protein and mineral matter for plant nutrition! Microbes break down these compounds and make them available to plant roots.

The earth teems with other forms of organic life — ants, beetles, spiders, rodents, to mention a few — Darwin estimated that the excretal matter from earthworms, insects and rodents was some ten tons per acre. More recent studies estimate it at about twenty-five tons. The Connecticut Agricultural Experimental Station found that earthworm castings were rich sources of nitrogen, phosphorus, potash, and magnesium. In comparison with the top soil, the castings contained five times as much nitrogen, seven times as much phosphorus, eleven times as much potash and three times as much magnesium.

Dead roots of old plants are also a rich source of organic matter. A two year crop of red clover supplies about three tons of dead roots per acre which contains about 180 pounds of nitrogen, seventy-one pounds of phosphorus and seventy-seven pounds of potash. Roots decay rapidly and the spaces which they occupied remain channels to aerate and irrigate the subsoil. Above ground residues of crops may contribute one to three tons of additional fertilizer per acre.

Rain washes into the soil about forty pounds of sulphur per acre per year. It also washes atmospheric dust, teeming with microbes, carbon and some lime into the soil to contribute more to its fertility. Even snow, which has been termed the "poor man's manure" has affinity for phosphoric compounds and is rich in nitrogen.

The subsoil rocks constantly undergo weathering to form new soil to offset the erosion of the surface soil. The loose rocks near the surface are valuable as fertilizer material, providing aeration and warmth for the plants growing in the topsoil.

Plants obtain only about five per cent of their nourishment from the soil. The other 95 per cent of their nourishment is obtained from the air, the sunshine and the water. Dr. Chlorophyl, the master chemist, traps the sun's energy, collects a few elements from the air and the soil, combines these with water and then plants fabricate the nutritional essentials for the growth of bacteria, fungi, earthworms, insects, reptiles, fowls, fish, animal and man. Directly or indirectly all life comes from the soil and we who live upon its surface should take a lesson from the earthworm — to use nutrient material for the synthetic processes which keep life going for the life span of the species, to deposit our excretal wastes in the topsoil and return our carcasses to the soil for re-use in the endless cycle of growth, decay and return.

III

It is the consensus among foremost thinkers that we must revise, reimplement and frequently reverse the direction of trends in our politics, husbandries, economy and culture. Since the problem of nutrition encompasses the Wheel of Life, then a revolution in nutrition could and will profoundly influence every aspect of our way of life.

Before we start this overdue revolution in nutrition, let us examine briefly what has occurred in one sector of our food culture to make this revolution desirable.

As you all know, the pioneers were not interested in the maintenance of soil fertility or the conservation of their soils. The customary procedure was to move into a section where Nature's Wheel of Life had been turning undisturbed for centuries, destroy forests wantonly, grow as many successive crops as possible before the soil became exhausted of its natural fertility, kill or trap game for the sport of it, and then to construct a flatboat and float downstream to settle and rape another fertile section of land. To a great degree, this profligate behavior was responsible for the western expansion of the pioneers. After the pioneer period the signal success of intelligent agricutural practices in the very deep South was noted and people gradually became rooted to the ground upon which they were born. A gradual transition in farming methods took place due to an increased demand for livestock and farm products, to insufficient and inefficient manpower, and to the necessity for maintaining the productivity of the soil. In response to the urgency of these factors, scientific and inventive minds began to develop technologic methods and machines which, within the past seventy-five years with the aid of the profit incentive and the help of a poorly disciplined embryonic advertising business, have succeeded in changing our food culture and economy.

Let us examine these changes and ask ourselves whether these practices have been beneficial or harmful.

Grains and cereals are our most abundant and predominant source of foods. In the pre-combine days, wheat was allowed to mature on the stalk. It was reaped by hand and shocked, threshed and sun-dried to reduce the moisture content so that spoilage while in storage would be minimized. Today the reaping and threshing of wheat is one operation and the moisture-laden grain is hauled to a storage bin where cyano gas is forced into the bins to protect the grain against the ravages of rodents, weevils, and other pests until it is milled between steel rollers, and bolted (literally filtered) through cloths of various gauges to separate

the component elements of the wheat berry into five commercial products. The flour is then treated with "agene" to improve its baking and keeping qualities. This chemical produces convulsions in dogs and other animals. Its effect upon humans is probably harmful; what will poison a dog will poison a human.

In 1840, one ounce of genuine unspoiled whole wheat bread made of whole stoneground wheat (not flour) contained 30 units of vitamin B_1. One hundred years later one ounce of white bread contained not 30, but FIVE units of vitamin B_1. Seven hundred units of vitamin B_1 per day are considered necessary for the maintenance of good health. The daily consumption of 40 ounces of whole wheat bread in 1840 assured 1,200 units of natural vitamin B_1 — while our average daily intake today assures only 200 units, mostly synthetic. Besides being robbed of vitamin B_1 the wheat berry is robbed of other known and unknown dietary factors — proteins, other important fractions of the vitamin B complex, vitamin E and a number of essential minerals. To produce commercial white flour, the removal of these essential nutrient factors is considered necessary in order to decrease spoilage and to produce profits. White flour is sold to the bread or bakery industries; part of the bran finds its way to the laxative-factories; part of the gluten is sold to the gluten-bread factories for consumption by diabetics; middlings are processed by the breakfast food and cereal factories to give the gullible their quota of morning "pep"; part of the wheat germ and wheat germ oil finds its way to the drug factories to be processed for pharmaceutical distribution where childless couples are urged to purchase it to restore their sex fertility — and most of this would be unnecessary if we ate foods as produced by nature. What is left of the wheat berry is then sold for livestock food. Other grains and cereals, including polished rice, are subjected to similar processing.

The consumers of bread and bakery products made from the bolted flours of grains and cereals have been assured that they need not worry because the wise food chemists have "enriched" these non-nutritious flours with a few synthetic vitamins and inorganic minerals. This assurance, in the form of widespread propaganda, is made in the face of contradictory evidence adduced by investigators having no direct or indirect vested interest in the manufacture or sale of synthetic vitamins or inorganic minerals.

Briefly summarized, the steel roller mill, mono-crop agriculture, failure to conserve the soil or replenish it with humus, the combine, cyano gas treatment, separation of grains and cereals into several fractions which are used and sold separately, the centralization of the milling industry in certain sections, the development of the baking industry, etc., have dangerously altered our food economy and culture with respect to breadstuffs. Sadly enough, instead of the consumer receiving nutritious bread products at a cheaper price he buys a starch product of dubious and unproven nutritive value which has to be enriched before it is considered fit to eat, and pays an exorbitant price for it.

As previously stated, 12 factors are involved between the field and the table to determine whether or not our nutrition shall be adequate or inadquate. Food should be judged on a quality rather than a quantity basis. Unfortunately few standards exist for informing the consumer as to the quality of the food produced. In view of the fact that the quality of our food involves so many factors, mostly disadvantageous ones, legislation is in order to enforce proper labeling and grading of all foods sold to the consumer. Date labels are greatly needed for all tinned and packaged foods. We as physicians should become active participants in urging the framing of a pure food and drug law which would be a positive agency in protecting the consumer. Also we should become interested in such vital problems as soil and water conservation, in fertility replenishment of soils with humus and fertilizer material processed from urban garbage, street sweepings and sewage, and in the climatic factors which so largely determine the biologic quality of our food supply.

The excellent work being done in England by Sir Albert Howard, Sir Robert McCarrison and the Panel Doctors of the County of Cheshire, and in this country by agricultural experimental stations in practically every state of the Union under the direction of Prof. L. A. Maynard and associates, Cornell University, Ithaca, N. Y., and by Professors W. A. Albrecht and Samuel Brody, University of Missouri, Columbia, Mo., has established a one to one correlation between healthy soils and healthy plants and of both to healthy animals and humans.

IV

Since the beginning of time mankind has been bedeviled by the problem of an adequate food supply. This uncertainty of his food supply was caused largely by unpredictable events over which he had no control. The process which we now know as civilization possibly resulted more from man's unremitting effort to secure for himself an adequate food supply than from any other single factor.

The part played by food in the maintenance of good health and in the prevention of epidemic plagues has long been known to the public. Those of us acquainted with the history of the development of the science of nutrition are at a loss to explain why it has taken so long for physicians to establish an "eye to eye" correlation between the relation of food to the health of animal and man. In the past only in isolated instances did physicians drop their medicine bags long enough to question the relation of faulty or deficient food to the physical ailments that they were treating. Even now, despite the numerous positive findings of nutritional research, the rank and file of physicians and dentists ignore the enormous therapeutic potential which is inherent in foods of good biologic value.

What food processing is doing to our national health was shown recently by a large-scale experiment. At the beginning of World War II someone in the Surgeon General's Office probably unfamiliar with the physical manifestations of malnutrition, drew up a list of physical specifications for use by the draft examiners. The rejection rate of the first two million selectees soared to a startling figure and a lower standard of physical fitness was formulated. Even so, draft rejection rates in World War II were approximately 14 per cent higher than those of World War I. These are cold figures that demand an answer and action from us as guardians of the nation's health. I do not think that this unfitness of our youth can be ascribed to a more universally potent factor than the increased consumption of highly processed foods which spiraled upward between 1918 and 1941.

All of you recall, I am sure, the economic debacle which occurred shortly after World War I and the familiar bread-lines, PWA projects, food stamps and other agencies of expediency which were resorted to in an effort to forestall widespread famine in this land of plenty. However, our food culture by this time had been so critically disturbed by the food industry, chiefly by the milling, baking, pie and cake making units, and by the sugar, candy, and sweet beverage manufacturers, that literally we fed the thousands of people on relief with cake and candy!

Paralleling this rise in malnutrition, of which most physicians were unfamiliar, we have seen a concerted drive for more hospitals, clinics, custodial institutions and for universal distribution of free medical care. These drives are masqueraded under the guise of health-promoting programs.

What are the factors responsible for this deplorable change in our food culture? The undermining of our national health began with the pioneers' practice of acquiring land, exhausting it and then abandoning it to the forces of erosion, etc. Later came the McCormick reaper, the steel roller mill and other processing innovations which were to become the foundation for many corporate units of the food industry. This centralization of the food industry, plus mass production, licked the small food merchant who had been selling locally produced, less processed foods than those now sold by grocers. The medical and dental professions failed to oppose the wholesale adulteration of our food supply, thereby allowing the insidious extension into our food culture of processed foods whose nutritional value was never questioned, until after the damage was done.

Conditioned food habits based upon biologically irrelevant traditions, prejudices fashions, prestige symbolisms and advertising slogans or programs unfortunately govern most of us in our choice of food.

How can the medical and allied professions become effective in combating the serious effects of malnutrition on public health?

1. We should interest ourselves in the soil; its fertility, its replenishment and conservation.

2. The problem of water conservation is also an important one.

3. We should educate our patients to insist upon buying natural foods rich in nutritive essentials, and to refuse to buy highly processed food commodities low in nutritive content. As a group, we could be instrumental in promoting an effective consumer boycott of these foods.

In the last analysis, food of good biologic value is the best therapeutic agent we possess. To this end this sketchy address was prepared.

Nutrition Notes

Mixed Insulin

There is some advantage, in certain cases of diabetes mellitus, of giving regular and protamine-zinc insulin mixed in the same syringe. Such mixtures produce effects appreciably different from those obtained by similar doses given as separate injections at different sites. Some preparations of PZ insulin contain an excess of protamine, and when any regular insulin is added, it will be altered, if not exactly to protamine-zinc insulin, to a compound which has a delayed action. Roughly, one unit of PZ insulin can adsorb and change one-half unit of soluble insulin. Each patient has to be considered individually and a combination found which works on his or her particular case. The regular insulin should be drawn into the syringe first and secondly the PZ insulin drawn into the the same syringe, and the syringe rolled in the fingers to assist mixture prior to injection. Such a method of treatment can be made to obviate nocturnal hypoglycemia, and usually only one injection daily is needed.*

Diet and Infection of the Eyelids

The time-honored methods of treating styes are not always successful and there is now some evidence to indicate that a poor diet, especially one which is inadequate in proteins, has much to do with predisposing to the infection and an adequate protein intake is essential in curing it. Unpublished reports on children living on the islands off North Carolina show an extremely high incidence of marginal blepharitis and styes and these children live on highly refined starches and grains with very little protein of animal

* Downie, E.: Observations on the use of mixtures of protamine zinc and regular insulins in the management of diabetes mellitus. Med. J. Australia, April 3, 1948, Vol. 35, No. 14, 425-429).

origin. A dietary investigation of children suffering from styes shows that those children who have the disease, irrespective of their financial status, subsist on a high carbohydrate and low protein diet. Cockrum et al.* present a good argument in favor of using a well-balanced protein intake as a primary step in treating styes without neglecting other well-known methods of therapy.

* Cockrum, W. M., Lynch, H. D., Slaughter, H. C. and Austin, E. W.: Styes: the role of nutrition in etiology and treatment. J. Ind. State Med. Assn., May 1948, Vol. 41, No. 5, 489-490.

Human Serum as Protein Supplement

Naturally the great obstacle to using human serum in conditions of protein deficiency, where food cannot be taken or retained by mouth, is the difficulty of obtaining sufficient supplies of the serum. Where food can be eaten or drunk, possibly the best food is milk because it can be given in really large amounts without the disadvantage of excessive fats. *Powdered skim milk* contains to each 100 grams, 37 grams of protein, 50 grams of carbohydrate and only one gram of fat. When made up with twice its weight of water, each pint contains 92 grams of protein and this is a good daily ration of protein. When intravenous feeding becomes necessary, human serum has certain advantages over casein hydrolysates (amino-acid preparations). Since serum can be given without increase in the nitrogen output, we may say that it has a "biological value" of 100 per cent, but the hydrolysates have the same biological value as casein itself, which is about 25 per cent. Serum has a protein content of six per cent as compared with the equivalent concentration of only three per cent in hydrolysates.

James Isbister of Sydney, Australia* showed that human serum brought about urinary secretion in a case of anuria following mercury poisoning, although the patient died of extreme renal and hepatic necrosis. A case of bacillary dysentery in collapse recovered through the use of intravenous human serum because this agent increased the blood volume. Nitrogen balance was achieved in a severe, acute case of ulcerative colitis by the same method of treatment, although of course the disease itself was not cured. Six and one-half liters of serum was successful in making it possible to do a palliative operation on an hour-glass stomach due to ulcer in a patient who then made a good recovery. In this case a large positive nitrogen balance was achieved.

If we think more about "non-surgical shock" as it occurs in severe infections, intoxications and in terminal states due to practical starvation, and if we further examine to discover how large a role is played in such cases by protein deficiency (lowered blood albumin levels) it will become apparent that perhaps human serum has no rival for its emergency value in raising the protein levels, combating shock and giving the moribund patient a chance for recovery, whether by surgical or medical means. There is a definite need in all countries for blood serum banks, and it is this need which the American Red Cross is striving to fill.

* Isbister, J.: Protein deficiency and the use of human serum in its treatment. Med. J. Australia, March, 20, 1948, Vol. 35, No. 12, 362-372.

How Much To Eat

Is the appetite a reliable gauge for measuring the correct food intake? Obviously not, since many persons never experience a feeling of satiety and are likely, for that reason, to eat too much and become too fat. There are others, particularly the "long-thins" who have never been on good terms with food merely because appetite is habitually absent; as a result they eat too little and tend to "play out" and come to the physician with a leading complaint of weakness which frequently is due to no organic disease but merely to the low caloric intake. It is difficult to curb the appetite of the individual who is always hungry but it is frequently quite impossible to confer an appetite on the one who never had any. Insulin works on some cases but not on all.

As a result of these two extremes of appetite we have two distinct kinds of people — one, who overeats and loses power as a result of the ill effects of adiposity and dies too young, and one who starves, remains thin and weak and lives too long. Those individuals who have a *moderate appetite*, do not get too fat, have enough "steam" and live long enough. Probably appetite originates in the brain and at present all we can say is that a disciplined mind, without evidence of libertinism which generates excesses, is likely to be situated in the happy mean. The people who do not like food probably do not like life. This is a broad statement requiring endless qualification, but clinical experience reveals that these enemies of food, who expect the physician to make them feel well, are of a type who devote their entire time to fretting, "stewing," planning and getting ahead in the world and no time at all to the pleasant task of sampling the multiplex pleasures of physical existence.

However it is not a case of *philosophy* with the thins — it is a case of constitutionality. And the fat people may have aversions to some of life's earthly pleasures, though not to eating. The two extremes — the woman with true *anorexia nervosa* and the happy fat man of decided extraversive tendencies — present insoluble difficulties at our present stage of clinical and psychological knowledge.

Actually there is very little to be done about it. It is interesting, though, that taking away food lessens appetite and giving food increases it. This truth — that to him who has, much shall be added, and its converse — opens a way for an attack, however marginal, on the problem. At the present moment there is evidence that some people who are not ill, are simply not getting enough calories to support their activities. We have had our attention focused so long on the "accessory food factors" that we sometimes forget to give some of our hopeful patients enough to eat. That is one matter which we ought to be able to attend to.

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 BEEF	EXCELLENT	FAIR	EXCELLENT	EXCELLENT	EXCELLENT
 LAMB	EXCELLENT	FAIR	GOOD	EXCELLENT	EXCELLENT
 VEAL	EXCELLENT	GOOD	GOOD	EXCELLENT	EXCELLENT
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Abstracts on Nutrition

HANSMAN, F. S.: *Proteins in health and disease.* (Med. J. Australia, Mar. 6, 1948,) V. 35, No. 10, 285-288).

The nature of proteins, how they are built up and the nature of the 23 primarily important amino-acids are described. The precursor of hypertensin is found in the alpha globulin fraction. Hypertensinogen is converted by renin, an enzyme produced by the kidney. Hypertensin is one important factor that controls blood pressure.

HEYMANN, W. AND HARTMAN, M. E.: *Hyperlipemia following intravenous infusion of hypertonic solution of sucrose.* (Am. J. Dis. Child., Jan. 1948, V. 75, No. 1, 68-75).

The effect of intravenous infusions of 40 cc. per kilogram of body weight of sucrose and dextrose solutions of various concentrations was studied on dogs. Repeated infusions of 10 to 15 per cent sucrose solutions may, and those of 20 per cent solutions usually lead to transient hyperlipemia, involving cholesterol, phospholipid and total lipid levels. At autopsy severe hydropic degeneration was noted in the kidneys of the dogs. Probably the hyperlipemeia observed is due to the damage to the renal parenchyma.

CADE, J. F.: *The anticonvulsant properties of creatinine.* (Med. J. Australia, Nov. 22, 1947, V. II, No. 21, 621-623).

In the course of some clinical experiments in connection with manic-depressive insanity, the author found, more or less by accident, that creatinine exerted a protective action against the toxic effects of urea on guinea pigs, doing away almost entirely with clonic and tonic spasms which otherwise characterize the experimental poisoning and preserving the animal's life. Preliminary clinical experiments, using creatinine in severe epileptics is definitely encouraging and the author points out the striking similarity between the graphic formulae of "dilantin" and creatinine.

THORLING, A. L.: *A case of "insuloma" with hypoglycemia.* (Nordisk Med., Jan. 30, 1948, V. 37, No. 5, 217-218).

A case report of a woman 34 years of age who during the past year had frequent attacks of delirium and also epileptiform seizures. During attacks, hypoglycemia was present, and the administration of glucose stopped all symptoms. Following a positive Whipple triad, operation was done for extirpation of the insuloma, and she has remained well during the four months since operation.

COX, J. E.: *The thyroid in gastroenterology.* (Rev. Gastroent., Feb. 1948, V. 15, No. 2, 111-118).

When an exhaustive examination fails to reveal disease in the gastrointestinal tract, one should, in the persistence of digestive symptoms, examine the endocrine system. Above all, a basal metabolic reading should be made, because hypo- or hyperfunction of the thyroid gland frequently is productive of dyspeptic syndromes.

STREICHER, M. H. AND PITTARD, V.: *Clinical studies of insoluble ketones as intestinal antiseptics.* (Proceed. Central Soc. Clin. Res., V. 20, p. 69, Nov. 1947).

Substances with anti-bacterial activity which are not absorbed from the intestine have the decided advantage of not giving rise to side effects. Insoluble ketones derived from para-amino-benzene sulfinic acid which have been shown to have anti-bacterial activity were tested on white mice and on patients. A ketone known as Nu 404 appeared to offer some promise as a useful clinical agent.

BALINT, P. AND KABDEBO, H.: *Premortal increase in the output of sodium and chlorine in fasting rats.* (Nature, V. 161, p. 57, Jan. 10, 1948).

Rats were fasted but given glucose solutions subcutaneously each day. Water was allowed ad libitum. In all cases on the last day before death the urinary output of sodium and chlorine was three to six times as great as on the previous days. The same results were obtained if urea was given subcutaneously instead of glucose or if the rats were not allowed free access to drinking water. The phenomenon is not regarded as absolutely fatal since administration of adequate food at the terminal part of the experiment permitted the animal to survive. No correlation between the onset of increased urinary output of sodium chloride and survival time (four to nine days) was found.

HEINLE, R. W., WELCH, A. D., GEORGE, W. L., EPSTEIN, M., AND PRITCHARD, I. A.: *Effect of extrinsic factor, liver extract, and folic acid on induced macrocytic anemia of swine.* Proceed. Central Soc. Clin. Res., V. 20, p. 7, Nov. 1947).

These workers have reported previously the production in the pig of a macrocytic anemia by administration of a folic acid deficient diet with crude folic acid antagonists included. The anemia is associated with megaloblastic hyperplasia of the marrow but there does not develop a histamine-fast achlorhydria.

Results of experiments on pigs suggest that the extrinsic factor and purified liver extracts are effective in this macrocytic anemia even though folic acid remains unavailable to the animal. Folic acid and its conjugates are not in themselves extrinsic factors since they are effective alone without the addition of intrinsic factor. Purified liver extracts which are effective in pernicious anemia may contain little or no folic acid.

To date there is no evidence that folic acid and the antipernicious anemia principle of liver function along any related chemical pathways.

HALDIN, J. AND WYNN, W.: *Blood sugar patterns of healthy adults after ingestion of large amounts of sucrose.* (Am. J. Physiol. V. 150, p. 263, August 1947).

In healthy adults the blood sugar curve following ingestion of sucrose (1.5 gm. per kilogram body weight, in 400 cc. of water) was identical as to onset and gradient, with that obtained after ingestion of glucose. The conclusion is drawn that the sucrose must be hydrolyzed very rapidly in the intestine and then absorbed as a hexose sugar.

JORDAN, R. A. AND CANUTESON, R. L.: *Hypothyroidism: a clinical study on students and personnel at Kansas University.* (Jour.-Lancet, June 1948, V. LXVIII, No. 6, 241-246).

Basal metabolic readings were made on 505 consecutive patients, mostly college students, and 67.3 per cent showed readings below minus 10, while 45.1 per cent showed readings below minus 15. This unusual finding of low metabolic rates may be related to the low iodine and high lime content of the waters of certain parts of Kansas. A high blood cholesterol reading increases the probability of hypothyroidism. Treatment of 161 patients with thyroid extract (U. S. P. two to three gr. daily) helped, as a rule, to relieve such symptoms as fatigue, menstrual disorders, nervousness, dry skin, brittle hair and a tendency to obesity.

QUIMBY, W. A.: *Pancreatin and some of its newer uses.* (Urolog. and Cutaneous Review, Dec. 1946, 743-745).

In the treatment of eczema, the use of pancreatin in moderate doses was found to be a valuable adjunct to the use of X-ray therapy, but the avoidance of carbohydrate in the diet is an essential part of the regime. Frequently local or general pruritus responds to similar treatment. The use of pancreatin in cases of food allergy sometimes cures even without avoidance of the causative food. Particularly valuable is pancreatin by the mouth in instances of radiation sickness or "roentgen nausea."

Editorial

THE CLINICIAN AND THE RADIOLOGIST

ACTUALLY, the work of a radiologist is extremely exacting, not only because of the technical difficulties in fluoroscopy and interpretation of films, but also because the patient's fate not infrequently hangs directly on his verdict. A case in point is the presence of a gastric cancer which, while heralding its presence by clinical signs and symptoms, eludes detection by the most careful roentgen examination. When a negative report is received by the clinician under these circumstances, it becomes the responsibility of the clinician to decide what to do. He may think best to advise immediate exploratory laparotomy or to have the X-ray studies repeated at an early date. As everyone knows, there are flat cancerous ulcers of the stomach which readily metastasize but may never be visible in X-ray films or under the fluoroscope. There are many times when the radiologist himself "believes" that a lesion is present in the stomach, but he has no choice but to report his findings as they are.

A negative X-ray report is frequently detrimental to the patient largely because the clinician fails to take his cue from it and proceed on his own judgment. This failure to rely on clinical signs and symptoms and the tendency to believe in the omniscience of the radiologist represents a natural development in medical practice. Prior to the present routine use of X-ray in diagnosis, physicians, relying on their own clinical judgment, developed a high degree of probability in their diagnoses. But so often did a *positive* X-ray finding completely close the case, that doctors developed an inferiority complex with respect to purely clinical diagnosis, and today it is rare to find the internist with sufficient courage of his convictions to cause him to regard roentgenology for what it is — an auxiliary service. All this applies equally to the clinical laboratory and its reports.

The stalwart clinician who relied upon his eyes, hands, stethescope, thermometer and brains, and did a good job, has practically vanished, and it is unlikely that he will ever return. His place is being taken, if it *can* be taken, by the well-informed and observant physician who realizes that today the diagnosis is partly machine-made and will so remain, but who has the wisdom never to accept a negative report without caution and who has the ability to weigh the increased quantity of evidence with an ever sharper acuity. Only through such wisdom and ability can the internist retain his present position in medicine.

Book Reviews

PERSONAL AND COMMUNITY HEALTH. By C. E. Turner, A.M., Ed.M., D.Sc., Dr. P.H. Eighth Edition. C. V. Mosby, Company, St. Louis, 1948, $4.00.

This book has proved itself valuable to a wide reader audience, having gone through eight editions in a dozen years. It is written particularly for readers at the university level and, in a sense, it is a "people's" practice of medicine, approached systematically, and from the angle of preventive medicine and hygiene. There can be no criticism of the factual material presented from the anatomical, physiological and pathological standpoint although the material as respects any given system is necessarily sketchy. The book should prove of interest to any layman who desires to obtain accurate knowledge of many of the disciplines concerned with health, particularly medical practice, and might well be recommended by the physician to those patients who want to go into "details" both from a practical and a general educational motive.

HUMAN BIOCHEMISTRY. By Israel S. Kleiner, Ph.D., Pp. 649, The C. V. Mosby Company, St. Louis, 2nd Edition, 1948, $7.00.

This is the 2nd edition and fourth reprinting of a book which has proved its usefulness and desirability to students of the human body and its diseases. Much of the success of this volume depends on the fact that the author conceives of biochemistry not as an isolated study but as an integral part of medicine. As he states, "the biochemist has come halfway from the laboratory toward the clinic." Each section bears witness to the attempt — one obviously successful — to surround the isolated biochemical fact with important and related clinical information. The sections on vitamins and foods are particularly happy. The volume is hereby unqualifiedly recommended to all students and practitioners of medicine.

SPECIAL NOTICE!

DDT POISONING A SERIOUS PUBLIC HEALTH HAZARD

MORTON S. BISKIND, M.D.
NEW YORK

Numerous cases of a puzzling syndrome, persistent, recurrent and debilitating, have recently appeared throughout the United States. Gastroenteritis with nausea, vomiting, abdominal pain and diarrhea occurs, as well as rhinitis, cough, a "constriction" or "lump" in the throat, intractable headache, giddiness, apprehension, pain, stiffness and aching of extremities and back of neck, and extreme muscular weakness. These cases are either undiagnosed, confused with other entities, or attributed to a hypothetical "virus X."

In more than 200 cases investigated by the author, the syndrome and repeated recurrences followed immediately on direct exposure to DDT (dichloro-diphenyl-trichloroethane). Although DDT is extremely toxic to all animals (being cumulatively stored in body fat), it is erroneously considered lethal only for insects and nontoxic to man. Its indiscriminate use in agriculture creates another hazard, as DDT now appears in food (verified by actual assay). Crops and animals alike are widely treated with DDT. It is no accident that findings in the new and often fatal "X disease" of cattle are (as in the human cases) identical with those reported in DDT poisoning.

This subject is considered at length in a forthcoming report *(American Journal of Digestive Diseases,* in press).

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN
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CLINICAL MEDICINE

BOWEL

McGUFF, P.: *Endometriosis as a cause of obstruction of the intestine.* (Proc. Staff Meet., Mayo Clinic, April 28, 1948, V. 23, No. 9, 215-221).

Endometriosis (the existence of endometrial tissue in any extra-uterine location) is frequently associated with such pelvic lesions as fibroids and ovarian cysts. Their appearance in the pelvis extra-uterinely or in the colon, recto-sigmoid or even the ileum, is probably due to lymphatic and venous metastases. Endometriosis may produce intestinal obstruction, for which the treatment is surgical. Diagnosis rests upon proctoscopic and X-ray examination, as well as noting a menstrual rhythm in the symptoms. The finding of a firm tumor in the rectovaginal septum or of tender palpable nodules plus the palpation of uterine fibroids and bilateral ovarian cysts, is suggestive of endometriosis as the cause when intestinal obstruction is present.

ODEL, H. M. AND FERRIS, D. O.: *Continuous lavage of the small intestine as a means of treating renal insuffiency: report of a case.* (Proc. Staff Meet. Mayo Clinic, April 28, 1948, V. 23, No. 9, 201-208).

In attempts to dialyze off urinary waste products in uremic states, all portions of the digestive tube have been used. In animal experiments dialysis was accomplished across the wall of the jejunum more adequately than in any other segment of the small intestine. In a young man with chronic glomerular nephritis and severe reduction of renal function, significant amounts of urea were removed by dialysis through the small intestine. However certain technical difficulties present themselves before this can be adopted generally as a method of treatment and the article should be consulted.

JANUS, W. L.: *Regional jejunitis.* (Radiology, April 1948, V. 50, No. 4, 532-535).

Three cases of proved regional jejunitis, one involving the duodenum, are described and it is surmised that this disease may not actually be rare. All cases were without fever and laboratory investigation was of no diagnostic value. The symptoms were anorexia, nausea, abdominal pain and loose stools. The diagnosis usually can be made by X-ray, by finding a definite disturbance of jejunal configuration. There is a loss of the fine feathery appearance, which is replaced by fuzziness and many spastic areas. There is increased motility of the barium in affected areas. The treatment is surgical, usually by some form of anastomosis. The affected bowel shows thickened, beefy walls and there are associated enlarged lymph glands which microscopically show simple adenitis. A chest film should always be taken to rule out tuberculosis.

BROWN, C. H., COLVERT, J. R. AND BRUSH, B. E.: *Clinical aspects of carcinoma of the cecum and ascending colon, (report of 60 cases).* (Ann. Int. Med., May 1948, V. 28, No. 5, 940-948).

Pain was present in 76 per cent of cases suffering from cancer of the cecum and ascending colon and was the predominant presenting symptom. Symptoms of obstruction appeared in 38 per cent, diarrhea in only 20 per cent An annular type of growth was found in 32 per cent and a constricting lesion in 25 per cent. The immediate post-operative mortality in the past five years has been eight per cent. Pain and obstruction are usually not considered as common as found in this series of cases.

BACON, H. E. AND HERING, A. C.: *Surgical management of congenital malformations of the anus, rectum and colon.* (J. Arkansas Med. Soc., July 1948, V. 45, No. 2, 41-46).

In a series of 98 cases presenting malformations of the anus and rectum alone, approximately 30 per cent disclosed additional defects, among the commonest of which were hypospadias, extrophy of the bladder and hare-lip and cleft palate. Surgical indications and methods are described.

CRAIG, M. S.: *Prevention of cancer of the rectum and colon: diagnosis and treatment of the pre-cancerous lesions.* (J. Arkansas Med. Soc., July, 1948, V. 45, No. 2, 46-49).

The author states, "It is safe to say that one of every six persons over 40 years of age will develop a pre-malignant tumor in his rectum or colon if he lives a normal span of life." Adenomas are to be sought by routine examinations of the rectum and colon. Possibly county cancer control groups should undertake this work.

ENGESET, A.: *Gangrenous pyoderma and ulcerative colitis.* (Nordisk Med., Feb. 7, 1948, V. 39, No. 27, 1295-1297).

A severe case of fatal gangrenous pyoderma is

described in a woman of 35 suffering from ulcerative colitis. The two conditions often run a parallel course for months and years. The author feels that a common infective link exists between the skin and bowel condition, although certain features of the gangrene speak against an infectious etiology.

MEYER, A. C. AND JUDD, E. S.: *Granulomatous tumor of the descending colon simulating carcinoma: report of a case.* (Proc. Staff. Meet. Mayo Clinic, June 23, 1948, V. 23, No. 13, 291-295).

The case described is one in which an inflammatory lesion surrounded the descending colon, producing partial obstruction and presenting every roentgen and gross appearance of carcinoma. The specimen microscopically showed a pathologic process somewhat similar to that seen in regional ileitis.

PANCREAS

GOIN, L. S.: *Fibrocystic disease of the pancreas.* (Radiology, July 1948, V. 51, No. 1, 36-41).

Fibrocystic disease of the pancreas accounts for four per cent of all infant deaths and has been overlooked because so much of its symptomatology arises in the lungs — bronchiectasis, atalectasis and bronchopneumonia. There is also diarrhea and fatty stools. X-ray films of the chest are necessary in the diagnosis. The reason for the constant chest involvement is unknown. Treatment is by vitamins (especially A), casein hydrolyzates and pancreatin as well as by efforts directed toward the cure of the lung condition.

SEVRINGHAUS, E. L.: *A psychomotor syndrome associated with a heterotopic pancreatic adenoma.* (Psychosom. Med., March-April 1948, V. X, No. 2, 109-110).

A case is reported of a woman with hypoglycemic convulsions cured by the eventual removal of a benign pancreatic adenoma in the spleen. Not only was she physically cured by the operation but a mental and emotional disturbance associated with the disease was also cured. Psychological tests indicated that her mental state was not psychogenic but associated with a gross brain lesion. She had bilateral positive Babinski signs and the encephalogram showed considerable air beneath the tentorium and mild bilateral cortical atrophy. It is felt that this atrophy resulted from her long continued hypoglycemia.

BAGGENSTOSS, A. H.: *The pancreas in uremia.* (Am. J. Pathol., 23, p. 908, Sept. 1947).

Studies of the pancreas were made on 270 cases in which there was uremia due to various causes. From 39 to 52 per cent showed lesions of the pancreas. These consisted variously of dilatation of the acini, flattening of the duct epithelial cells, insipissation of intraacinar secretions, and loss of zymogen granules in involved acini. Acinal involvement was not limited to any particular part of the pancreas and not associated with obstruction of the ducts. The age, sex, duration of the uremia, and the degree of azotemia, did not appear to be significant. Baggenstoss thinks that the probable cause of the pancreatic lesions is dehydration in association with some unknown metabolic disturbance.

LIVER AND GALLBLADDER

BROOKS, C. D., CONNOLLY, P. J. AND MURPHY, R. T.: *The management of cholecystitis.* (Harper Hosp. Bull., May-June 1948, V. 6, No. 3, 68-73).

When stones were seen by X-ray the authors subsequently found them in 100 per cent of cases operated on in the past five years, and no stones were found in any case in which the X-ray was negative for stones. However stones were found in 86 per cent of gallbladders not visualized by X-ray and in 67 per cent of those with impaired function. They feel that patients should not be subjected to surgery who do not have stones by X-ray, and who also lack a history of local or referred pain, chills and fever, or definite spasm. When indicated surgery is not carried out such serious complications as rupture, peritonitis, hepatitis and pancreatitis may follow. Gallbladder cases get out of bed the day following surgery.

DAMODARAN, K.: *The liver in infective hepatitis.* (Brit. Med. J., June 5, 1948, 1079-1082).

Liver changes in fatal cases of infective hepatitis vary from acute necrosis to portal cirrhosis depending upon how long the patient lives. If death occurs in two weeks the findings are those of acute necrosis. After three months, the pattern of portal cirrhosis is obvious. Such a sequence occurs in less than one per cent, the balance of the cases ultimately recovering.

KING, W. E. AND PERRY, J. W.: *Technique of aspiration biopsy of the liver with reference to its use in diagnosis and prognosis.* (Med. J. Australia, June 5, 1948, V. 35, No. 23, 697-701).

A full description is given of the technique employed in doing aspiration biopsies of the liver, employing the Franseen needle. The two complications most to be feared are hemorrhage from the liver and perforation of the bowel. The clotting power of the blood is increased by the routine use of vitamin K and a flat film of the abdomen is made to observe the position of the intestinal coils. The mortality of the procedure varies from zero to about one per cent, nevertheless it should never be undertaken lightly. Study of the liver column obtained is invaluable in diagnosis and sometimes there is no other way of making a diagnosis.

CULVER, G. J. AND KLINE, J. R.: *Acute gaseous cholecystitis.* (Radiology, April 1948, V. 50, No. 4, 536-538).

A case of gaseous cholecystitis is reported in which

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the diagnosis was made by plain X-ray film taken in the gall bladder region. This revealed the organ distended by gas with gas also penetrating the layers of the gall bladder wall. He made a good recovery on conservative treatment with penicillin and sulfadiazine. In these cases, which fortunately are rare, it is an error to operate as this usually leads to death. The gas is due to anerobic microorganisms. Where the gas is of intestinal origin, the bile passages can be seen containing gas.

JORGENSEN, G.: *Gallstones in feces.* (Nordisk Med., April 9, 1948, V. 38, No. 15, 744-745).

1. The presence of gall-stones up to the size of a nut in faeces is a sure symptom of choledocholithiasis.

2. In my material comprising 122 possible and 53 certain choledocholithiasis patients, stone was found in faeces in 20 cases, i. e. in 16 and 37%.

3. In two trial groups of 10 patients in all there was present a total of 35 gall-stones. Of these 30 (86%) were found in the stools. It may therefore be supposed that by far the greater number of stones delivered to the intestines can be detected by careful examination.

In the first trial group there were seven patients with no stomach, intestinal or liver suffering. These patients were given shellac-coated stones to avoid the action of the stomach juices.

In the second trial group there were three patients with achylia. These patients were given stones without coating.

The result in the two trial groups agrees.

4. A number of the stones given in the above trials bear clear signs of having been subjected to resorption, which was greater the longer the stay in the intestine had been. Some stones were probably resorbed.

5. It will be of importance in carrying out systematic investigation for gall-stone in faeces to give the patients laxative medicine at the same time, e. g., Carlsbad salts, as in that way owing to the quicker passage through the intestines it is possible to decrease the resorption.

RYSSING, E.: *Residual infectious hepatitis.* (Nordisk Med., April 9, 1948, V. 38, No. 15, 737-739).

A brief survey is given of the literature concerning the post-icteric period and previous follow-up examinations of patients apparently recovered from hepatitis. Attention is called in particular to the frequency of long periods of convalescence.

In the present follow-up studies an account is given of the fate of 208 patients previously hepatitic.

In 171 previous patients with an observation period of five to eight years the only sequelae observed were an uncharacteristic dyspepsia in 20 (five males, 15 females) and urobilinuria in three.

Altogether 11 patients thought that they had had an attack of jaundice after discharge from the hospital. Recurrence of the lesion was ascertained in two cases, unquestionably new hepatitis in five, probable cholelithiasis in two, and dubious icterus in two.

The distribution curve for serum bilirubinuria was found to be the same as obtained in normal subjects though with a lower average — probably because the blood was extracted late in the afternoon. The serum bilirubin concentration did not increase in any instance.

The thymol test gave no definitely increased values.

The Takata reaction was negative in every instance.

Enlargement of the liver or spleen could not be ascertained in any instance.

YTREHUS, O.: *Telangectasis hemorrhagica heriditaria and liver cirrhosis.* (Nordisk Med. April 9, 1948, V. 38, 730-733).

The author mentions a case of Osler's disease with hepatic affection in a 54 year old woman. Following an acute jaundice in April 1940, her Osler's disease was obviously aggravated, with eruption of telangiectases and frequent bleedings from the nose. The patient died under a picture of hepatic cirrhosis. At the post mortem a hepatic cirrhosis was found, closely resembling Laennec's type but with telangiectatic dilated vessels both in the liver, the heart, the nasal mucosa and the brain. Two of the brothers and sisters of the patient have also been examined and showed symptoms of latent hepatic affection with slightly increased serum bilirubin and an increased amount of lipases in the blood, resistant to quinine. Various opinions regarding the etiology of Osler's disease are briefly mentioned. As of prac-

tical importance it is pointed out that the hepatic affection may pass unnoticed and that telangiectases may exist as long as 15 to 20 years before any clinical manifestations of the liver disease. As is also pointed out by American authors, one is therefore advised to be cautious with hepato-toxic drugs in patients with telangiectases.

ULCER

SCHWARTZ, L. A.: *Psychosomatic aspects of peptic ulcer.* (Harper Hosp. Bull., Feb. 1948, V. 6, No. 1, 11-17).

This is an attempt to clarify our conceptions and terminology with respect to the influences of emotional states in the production of gastric hypersecretion and possibly of peptic ulcer. At first we felt that psychic trauma adversely affected an existing ulcer, but now we more or less accept the view that psychic disturbances actually cause the ulcer. Draper's idea that *fear,* usually based upon an increased femininity content in the ego of the predominantly "male" ulcer patient, is perhaps merely another way of expressing Alexander's theory of repressed oral-receptive tendencies. This theory is built upon the finding of a conflict in the deeper layers of the ego quite beyond the limits of consciousness, common to ulcer patients. The conflict is caused by a deep desire to be dependent upon someone (mother, mother-surrogate) or *to be loved,* failing which in actual experience, the ego regresses to the infantile equivalent, viz., *to be fed.* This arouses gastric activity, occasioning hypersecretion and possibly causing peptic ulcer. It must be pointed out that this kind of hypersecretion and increased gastric activity is by no means the same thing as appetite secretion, which is a conscious process, although presumably it would be mediated largely through the autonomic nervous system. The entire problem is by no means clearly delineated at this time. On more superficial levels of the ego, we know that emotional stress, anxiety, insecurity, resentment, guilt and frustation as well as fear are capable of producing gastric hyperactivity, but there is also good evidence that different individuals may and do react differently to such stresses. Nevertheless, the recent work of Mittelman and Wolff show conclusively for the first time a simultaneous augmentation of acid-pepsin secretion and motor activity of the stomach accompanying certain emotional reactions. These should be placed in the category of the cephalic phase of secretion although they have no relation to the taking of food or the conscious thought of taking food, and no relation either to basal secretion. It is possible that more fundamental progress in the therapy of ulcer will result from increased study of the affective states.

STEINBERG, N.: *A new protein hydrolysate for the treatment of peptic ulcer.* (Rev. Gastroent., April 1948, V. 15, No. 4, 319-332).

The author merely states that his protein hydrolysate was "prepared from a combination of a vegetable ferment (papain) with yeast complex, and enzymes on defatted soybean flour." The use of this preparation stopped ulcer pain in all cases within two or three days. Its high neutralization factor makes the

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hydrolysate a valuable adjunct in peptic ulcer therapy. The addition of five per cent whole protein serves best to control epigastric pain and vomiting in pyloric block. Mixed with olive oil, as an emulsion, it serves well for interval feedings during the night.

MALMROS, A. H. AND HIERTONN, T.: *The life-cycle of peptic ulcer.* (Nordisk Med., April 16, 1948, V. 38, No. 16, 774-778).

This report includes 687 cases (195 gastric and 495 duodenal ulcers) all diagnosed by X-ray and followed up from seven to ten years; only 0.6 per cent could not be followed up. Medical treatment consisted of three or four weeks in bed in hospital with diet and antacids. Although 93.5 per cent showed cure by X-ray, the late results were bad. A grave course was shown in 40 per cent of cases and a satisfactory course only in 31 per cent, the balance showing "fair" results. Duodenal ulcers have the greater tendency to relapse. Emotion, fatigue, lack of sleep and infection are enemies of peptic ulcer patients. If the patient cannot be controlled, operation should be done early. Billroth I operations showed a 65 per cent excellent subsequent course, and the operative mortality was low.

HIRSCHBERG, A. F.: *Medical management of peptic ulcer.* (Nordisk Med., April 16, 1948, V. 38, No. 16, 771-774).

Hitherto the author considered medical treatment of ulcer as effective as any treatment in the realm of medicine, but recent statistics are admittedly discouraging. He divides peptic ulcer into *constitutional* and *exogenic* forms. The prognosis is best in those with short histories, although there is no reliable protection against recurrences. Long-continued diet, and avoidance of physical and mental strain as well as respiratory infections constitute prophylaxis. The patient must be convinced of the importance of the diet, otherwise it becomes burdensome and disheartening. Laborers, who have to work hard, should be treated surgically. Psychosomatic medicine in its emphasis on reduction of psychic strain has done good, but there is a danger of psychosomatic medicine becoming too one-sided.

CRILE, G. JR., AND DEMPSEY, W. S.: *Treatment of gastric ulcer.* (Cleveland Clin. Quart., July 1948, V. 15, No. 3, 147-151).

It is not always possible to distinguish between peptic ulcer and cancer of the stomach. Most cases of gastric ulcer requiring operation should be treated by gastric resection rather than by vagotomy. Vagotomy for gastric ulcer is not recommended unless (a) the ulcer is excised and examined microscopically or (b) the ulcer is so high that it cannot be resected without performing a total gastrectomy or incurring undue risk.

JAMES, C. W.: *Peptic ulcer in pregnancy: with report of a case of perforation.* (Brit. Med. J., July 10, 1948, 74-75).

The author's case developed a perforation of a duodenal ulcer in the 36th week of pregnancy. The discussion deals with the question — why is peptic ulcer so extremely rare in pregnancy? No definite conclusion could be reached. The fact that the secretion of gastric acid varies inversely with the concentration of gonadotropic hormone in the urine suggests that a new method of treatment for ulcer might be established rivaling vagus resection in popularity. The work of Sandweiss is referred to, (Amer. J. Obst. Gynec., 45, 131).

STRAUS, D. C.: *Vagus nerve resection (vagotomy) in the treatment of acute perforated duodenal ulcer: report of a case.* (J. Indiana State Med. Assn., July, 1948, V. 41, No. 7, 700-703).

A man of 40 suffering from a very chronic duodenal ulcer was operated on for perforation, and because of his good condition, the incision was extended to permit bilateral transabdominal vagotomy. His recovery was rapid and four months after operation he was perfectly well and able to eat almost all kinds of food. This is the first case in which vagotomy has been employed at the time of a repair of a perforating peptic ulcer and the author feels that, owing to the frequently bad course following such repair, the vagotomy ought to be included in cases in which the patient's condition permits it. No general peritonitis was present.

JOHNS, T. N. P., AND GROSE, W. E.: *Symposium on vagotomy for peptic ulcer II. Early surgical results in 43 cases.* (Bull. Johns Hopkins Hosp., 81, p. 92. August 1947).

Vagotomy for peptic ulcer was performed on 43 patients with one death not related to the vagus section. Satisfactory results were reported in 34 of 41 patients followed for two months to two years; unsatisfactory results, making the operation a failure, were shown in seven patients. The failures were in patients who had had vagotomy alone without additional gastric surgery; on the other hand best results were obtained in 10 patients who had had pyloroplasty or gastroenterostomy in addition to vagotomy.

Transient bothersome effects were found in many of the "satisfactory" group and consisted mainly of increased bowel frequency and (or) diarrhea, sense of overwhelming fulness after eating, and sometimes vomiting. In 24 patients there was in effect a more or less marked paralysis of the stomach musculation.

DDT Poisoning and the Elusive "Virus X:" A New Cause for Gastro-Enteritis

By

MORTON S. BISKIND, M.D.

NEW YORK

DURING A PERIOD of more than two years, numerous cases of a curious symptom complex, apparently never before reported, have been observed throughout the United States. For want of a satisfactory explanation for this ailment, it has been widely attributed to infection with a thus far illusory "virus X."

The syndrome consists of a group of or all the following: Acute gastroenteritis occurs, with nausea, vomiting, abdominal pain, and diarrhea usually associated with extreme tenesmus. Coryza, cough and persistent sore throat are common, often followed by a persistent or recurrent feeling of constriction or a "lump" in the throat; occasionally the sensation of constriction extends substernally and to the back and may be associated with severe pain in either arm. In some cases the hyoid bone becomes acutely painful to pressure for a few days. Pain in the joints, generalized muscle weakness and exhausting fatigue are usual; the latter are often so severe in the acute stage as to be described by some patients as "paralysis." Sometimes the initial attack is ushered in by vertigo and syncope. Intractable headache and giddiness are not uncommon. Occasionally herpes zoster appears. Paresthesias of various kinds occur in most of the cases; areas of skin become exquisitely hypersensitive and after a few days this hyperesthesia disappears only to recur elsewhere, or irregular numbness, tingling sensations, pruritus or formication may occur. Erratic fibrillary twitching of voluntary muscles is common. Usually there is diminution of vibratory sense in the extremities.

After subsidence of the acute attack, irregular spasm of smooth muscle throughout the gastrointestinal tract often persists for weeks or months, associated with increased fatigability, which only gradually regresses. Febrile reactions occur occasionally during the initial stages but are not the rule. Except for a tendency to anemia, and in some cases a relative lymphocytosis, no constant changes are observable in the blood. Many of the patients have an acute bout of apprehension associated with the foregoing symptom complex and rarely is this relieved by reassurance as to the absence of physical findings sufficient to account for the severity of the disturbance.

Most striking about the syndrome is the persistence of some of the symptoms, the tendency to repeated recurrence of others over a period of many months (some patients fail to show complete recovery even after a year) and the lack of detectable lesions sufficient to account for the severity of the subjective reaction.

The high incidence, the usual absence of a febrile reaction, the persistence and erratic recurrence of the symptoms, the lack of observable inflammatory lesions, and the resistance even to palliative therapy, suggested an intoxication rather than an infection. Investigation for possible etiologic agents soon led to consideration of DDT (2, 2 bis (para-chlorophenyl) 1, 1, 1-trichloroethane; less precisely designated dichlorodiphenyltrichloroethane). The epidemic first appeared at about the time DDT came into widespread use by the civilian population. The signs and symptoms described in the pharmacologic and toxicologic literature as characteristic of DDT poisoning, are identical with those appearing in patients with the affection described (1, to 13).

Thus, among the disturbances which occur in known clinical poisoning with DDT are the following: acute gastroenteritis with nausea, vomiting, and abdominal pain, and diarrhea, coryza, cough, conjunctival irritation, a feeling of constriction in the throat and chest, dyspnea, persistent sore throat, giddiness, anxiety and apprehension, extreme lassitude, muscle weakness, fibrillary, spastic and even convulsive contractions of voluntary muscles, heaviness and aching of extremities, pain in joints, dermatitis, anemia, changes in the white blood cells and increase in blood calcium. In fatal cases of clinical DDT poisoning, tissue changes identical with those found in experimental poisoning in animals have been reported: degenerative changes in liver, kidney, spleen and adrenals, gastritis and enteritis with petechial hemorrhages throughout the gastrointestinal tract and hyperplastic changes in lymphoid follicles and Peyer's patches; pulmonary edema, bronchopneumonia, and changes in the blood vessels and cardiac musculature have also been reported.

Despite the fact that DDT is a highly lethal poison for all species of animals, the myth has become prevalent among the general population that it is safe for man in virtually any quantity. Not only is it used in households with reckless abandon, so that sprays and aerosols are inhaled, the solutions are permitted to contaminate the skin, bedding and other textiles are saturated, and food and food utensils are contaminated, but DDT is also widely used in restaurants and food processing establishments and as an insecticide on crops. Cattle, sheep and other food animals are extensively dusted with it and large areas are indiscriminately sprayed from airplanes for mosquito control. DDT is difficult and usually completely impossible to remove from contaminated foods (it is not affected by cooking) (14), and it accumulates in the fat and appears in the milk of animals who feed on

sprayed pasture or on contaminated fodder or who lick the DDT from their hides (14, to 16). As DDT is a cumulative poison (in animals repeated small doses are as lethal as single large ones) (17, to 20) it is inevitable that large scale intoxication of the American population would occur. In 1944, Smith and Stohlman (17) of the National Institute of Health, after an extensive study on the cumulative toxicity of DDT, pointed out, "The toxicity of DDT combined with its cumulative action and absorbability from the skin places a definite health hazard on its use."

Since low grade chronic intoxications from small amounts in foods are extremely difficult, if not impossible to trace, an effort was made to determine whether severe acute attacks of the type described could be related to known exposure to DDT. Patients complaining of the acute symptoms were therefore questioned as to prior exposure to this agent. A few illustrative cases are presented briefly:

Two patients developed acute gastroenteritis while at a vacation resort where kitchen and dining room were treated to frequent doses of DDT with an electric-powered aerosol device. In one of these patients, coryza and acute spasm of the lumbar musculature occurred at the same time. This was followed by a persistent sense of constriction and a feeling of a lump in the throat so severe that investigation was made for a possible neoplasm — none was found. Both these patients had subsequent repeated attacks of enteritis over a period of months and complained of continuous extreme fatigability, fibrillary twitching of muscles, irregular paresthesias and pain in the extremities. Eleven months later, some of the symptoms, while considerably less severe, were still present. One of these patients, some months after the original attack, was unknowingly exposed directly to a DDT aerosol used in a room connected by a partially open window with the room in which he was working. Within an hour there was recurrence of the sense of pharyngeal and substernal constriction, followed by nausea and abdominal discomfort. The next day the patient had coryza and diarrhea. Subsequently, both patients were exposed to DDT residues in an area that had been heavily sprayed. There was severe and persistent recurrence of all the symptoms in both cases.

Twenty-five patients with the "virus X" syndrome, were exposed directly to DDT spray or aerosol used to protect clothing from moths in a closet. In each case, within a few hours there was coryza, cough and conjunctival irritation to be followed next day by extreme debility, nausea, vomiting and diarrhea. The gastroenteritis persisted in each case for from one to four weeks, and increased fatigability, irregularly recurring malaise and other symptoms persisted for some months.

Twelve patients slept in beds sprayed with DDT at regular intervals (purely as a preventive measure — none had had bedbugs). Bedding, mattress and springs were indiscriminately saturated. All had repeated attacks of gastroenteritis with intervening intervals in which the main complaint was a disturbing sense of malaise. This is of interest in view of experimental poisoning in animals produced by contact with textiles saturated with DDT (17).

Another patient made a series of airplane flights to various parts of South America. During this trip he was repeatedly exposed to DDT aerosol used at a number of airports to prevent international transport of mosquitoes. In each case there was almost immediate irritation of the respiratory tract (other passengers complained of this too), with a sense of suffocation, cough and coryza, and giddiness. The patient's trip had finally to be interrupted when he developed a severe acute gastroenteritis and extreme muscular weakness requiring bed rest for 16 days. The enteritis, for which no etiologic agent could be found, persisted for weeks despite intensive therapy with sulfonamides, antibiotics and adsorbing agents.

In another case, while transferring a solution of DDT in kerosene from a spraying device to another container, the solution was spilled on the hands and not immediately removed. A residue of the original DDT solution contaminated the liquid subsequently used in the spraying device and to this the patient was also exposed. Acute gastroenteritis developed the next day; this persisted for two weeks. During this time coryza, sore throat and cough developed which subsided three weeks later. Extreme lassitude, pain in the joints and a disturbing sense of malaise persisted for weeks afterwards.

A patient with nutritional macrocytic anemia in whom the blood picture and nutritional state had been maintained for many months on adequate dosage of B vitamins, including folic acid, and liver, began to work weekends at an institution where she also took her meals. The patient noted that she invariably had a low grade nausea, occasional diarrhea and a sense of malaise, during and immediately following each of these weekends, but she dismissed these symptoms as possibly due to anxiety. When seen after several months of this regime, there was recurrence of the anemia despite continuation of previously adequate therapy. On inquiry it was found that the kitchen and dining room of this institution were regularly sprayed with DDT. The patient discontinued this employment and had no further attacks of gastritis though some malaise persisted and the anemia responded only very slowly to more intensive therapy.

Another patient in whose home DDT sprays were regularly used, had had repeated attacks of nausea, vomiting and diarrhea over a period of months and on several occasions was confined to bed owing to severe pain in the joints, muscular weakness, irregular paresthesias, and malaise. These attacks were invariably associated with severe apprehension.

In two further cases, patients working in an establishment where stored textiles were regularly sprayed with DDT for moth-proofing purposes, developed repeated attacks of gastroenteritis which persisted in each case for more than a month and was un-

responsive to any therapy. One of these patients, skeptical of any possible connection between her previous attacks and exposure to DDT, subsequently deliberately exposed herself to a DDT spray: nausea and severe abdominal pain supervened within a few hours, and diarrhea occurred subsequently. Two other skeptics who had had previous attacks of the syndrome described, re-exposed themselves, one to skin contamination with DDT solution, the other to DDT aerosol; both had prompt and severe recurrences which persisted for many weeks.

Altogether data have been accumulated on more than 200 cases of the "virus X" syndrome in which the condition followed immediately on known exposure to DDT.

On routine questioning of patients with the "virus X" syndrome as to exposure to DDT, I was surprised to find that more than a few of them had discovered for themselves that exposure to DDT spray or aerosol caused lachrymation, coryza, cough, "wheezing" and nausea. But all of them, completely convinced of the utter safety of DDT, dismissed these symptoms as unimportant.

As already indicated, a prominent feature in virtually all the patients was extreme apprehensiveness. This is probably explicable on the basis of functional and possibly even morphologic changes in the central nervous system produced by DDT, since in DDT poisoning in animals such disturbances are frequent.* This apprehensiveness (also reported in experimental DDT poisoning in man by Wigglesworth (1) and by Case (2) often made care of these patients extremely difficult since they were importunate both about diagnosis and the demand for relief. Infection with a hypothetical virus was distinctly unsatisfying as an explanation and no therapy appeared in any way to modify the course of the affection.

In some of the cases attributed to "virus X," observed at different times in different parts of the country, concomitant infection with actual known viruses, such as that of influenza and the common cold, is of course possible. This may have been responsible for failure thus far to consider the possibility basically of a toxic rather than an infectious agent.

DISCUSSION

The toxicology of DDT has been investigated extensively in a large number of species (17, to 24). It has been found almost without exception to be lethal to every form of animal life tested, the only limiting feature being the waxy nature of DDT and its solubility only in lipoids and lipoid solvents. It is largely this limited solubility which has been depended on (excessively, it now appears) to safeguard man and other mammals from poisoning.

In rats, mice, rabbits, guinea pigs, cats, dogs, chicks, goats, sheep, cattle, horses and monkeys, DDT produces functional and degenerative changes in the liver, gall bladder, kidney, spleen, thyroid, adrenals, ovaries, myocardium, voluntary musculature, central nervous system and peripheral nerves, gastrointestinal tract and blood (with variations depending on the species) (17, to 24). DDT is as lethal in repeated small doses as in larger single doses. In low-grade chronic poisoning in animals growth is impaired (20). The severe liver damage that results in these animals is not affected either by adequate protein (17) or by choline (20). In chronic administration by mouth no difference in toxicity is detectable between use of DDT in oil solution or in dry form (20). In chronic intoxication in rats there is a tendency to tumor formation in the liver (20). DDT is stored in the body fat and is excreted in the milk of dogs, rats, goats and cattle (15, 16).

Following an initial peak, excretion of DDT in the urine reaches a plateau and continues thereafter at a slow rate (18, 25); thus cumulative poisoning with DDT can and undoubtedly does occur with ease. DDT is demonstrable in the blood, bile, liver, kidney and central nervous system, as well as in the urine, in both acute and chronic poisoning (17), despite imperfect absorption. In cattle, eating of fodder contaminated with DDT residues in very small amounts, leads to storage in the muscles in amounts chemically detectable five weeks after discontinuing ingestion of DDT (14). Therefore, in addition to direct exposure to DDT powders, sprays and aerosols, cumulative poisoning in human beings is possible from ingestion of meat, milk, butter and other foods contaminated with traces of DDT.

Based partly on the military use of DDT, partly on acute studies on a small number of healthy adult volunteers and on limited observations of workers handling DDT, the misapprehension is widely current that DDT is lethal only to insects and is completely safe in all its forms for almost any insecticidal use by human beings. As a source of accurate toxicologic data, the military field experience with DDT leaves much indeed to be desired. Clinical syndromes of the type here described are hardly treated with sympathetic attention when occurring among soldiers in wartime. Questioning of returned veterans reveals that these reactions actually occurred frequently among soldiers exposed to DDT, but were invariably attributed to other causes. Unfortunately, the areas in which the heaviest treatment with DDT was required, are also the areas in which enteric infections especially are highly endemic.

This leaves then the investigations on human volunteers. Altogether comprehensive reports on five adult male volunteers were found in the literature; these volunteers were exposed to cutaneous absorption and ingestion of DDT solutions and inhalation of DDT aerosols. Of these five, three were investigated in Britain and two in the United States. In one case reported by Wigglesworth (1) brief application of

* Needless to say, findings related to the nervous system, and muscular spasm and weakness in severe acute affections of this type, have led to confusion with such entities as meningitis and poliomyelitis.

a solution of DDT in acetone to the skin, led to heaviness and aching of limbs and weakness of legs, "extreme nervous tension" and anxiety, insomnia and involuntary tremors of the whole body; anemia, leucocytosis and temporary rise in blood calcium occurred. Bed rest was required owing to pain in the extremities. The subject was away from work for 10 weeks and at the end of a year recovery was not yet complete.

Case (2) reports his own experience and that of a colleague, who exposed themselves to cutaneous absorption by direct contact with walls covered with a water-soluble paint containing two per cent of DDT and subsequently treated with a thin film of oil to simulate service conditions in the navy:

"The tiredness, heaviness, and aching of the limbs were very real things. and the mental state also was most distressing. Not only was a state of extreme irritability present, but also both subjects had a great distaste for work of any sort and a feeling of mental incompetence in tackling the simplest mental task . . . The joint pains were quite violent at times . . . subject A. I. was so prostrated he had to take to his bed for a day."

Other findings were increase in erythrocyte destruction, decrease in mean corpuscular hemoglobin, increase in reticulocytes, diminution in granulocytes accompanied by appearance of immature leukocytes, appearance of indican in the urine, diminution of some reflexes, and in one of the subjects, patchy anesthesia of the skin, slight impariment of hearing and transitory yellow vision, and muscular fibrillation. Recovery required from four to five weeks.

The American subjects were made of sterner stuff, for extensive inhalation of DDT aerosol (and in one of the subjects, subsequent ingestion of an oil solution of DDT), according to Neal, von Oettingen and their collaborators (26, 27), led to no significant untoward results. But even in these subjects diminution in hemoglobin from 19 to 15.5 gm. per 100 cc. occurred in one and a decrease of from 15 to 13.5 gm. in the other. Temporary irritation of the conjunctivae and respiratory tract, clumsiness and forgetfulness also occurred but these were attributed mainly to the vehicle in which DDT was dissolved. One of these subjects, as already indicated, twice subsequently ingested solutions of DDT in olive oil without ill effect (25). Yet Thoungh (7) has reported 27 cases of acute gastroenteritis with vomiting, diarrhea, giddiness and bradycardia following ingestion of rice accidentally contaminated with DDT powder, a form in which it is claimed to be less readily absorbed.

A survey of the literature reveals at least 46 known cases of DDT poisoning in human beings (1 to 12 to 28 to 30 to 32). The actual total is undoubtedly larger but indefiniteness in some of the reports does not permit of an accurate estimate. Sources of the DDT varied from actual ingestion of lethal quantities in solution, to exposure to DDT spray and aerosol, DDT paint and DDT residues on food. Six of the reported cases are known to have been fatal. The course of some of the other cases is not reported beyond the initial attack. In this investigation another fatal case undoubtedly due to DDT came to light. A young man who handled a large amount of DDT used mainly for dusting cattle, developed an intractable and rapidly fatal hemorrhagic gastroenteritis and hepatitis. The condition was attributed to an infection of unknown origin.

To anyone with even a rudimentary knowledge of toxicology, it exceeds all limits of credibility that a compound lethal for insects, fish, birds, chickens, rats, guinea pigs, rabbits, dogs, cats, goats, sheep, horses, cattle and monkeys would be nontoxic for human beings. The claims made by various investigators that DDT is safe for human beings were of course based on the assumption that the amounts to which persons would be exposed would not exceed the then known limits of tolerance. These limits did not take into consideration sensitization phenomena† or the tremendously wide variation in susceptibility to such toxic agents in the general population. Most of the exposed subjects examined have been healthy male adults, qualifications possessed by only a portion of the total population. But even the proposed safe limits have been exceeded.

Cameron and Burgess (33), for instance, considered solutions not to exceed 0.5 per cent of DDT safe for human use and pointed out that higher concentrations would be dangerous. Yet not only do the commercial preparations on the American market range mainly from three to 10 per cent, but they have been released for indiscriminate use by the general public, who in turn have been subjected to a barrage of dangerous misinformation on the subject. Even the 0.5 per cent solution advocated by Cameron and Burgess cannot be used safely by untrained persons, since even this concentration may be lethal to animals (34) and would undoubtedly be at least toxic to human beings.

Among the studies on the toxicology of DDT, two are of especial interest. Riker and his associates (35) and Jandorf, Sarrett and Bodansky (36) have both shown that DDT increases the oxygen consumption of body tissues. There is an increase in the metabolic rate of DDT-treated rats resembling somewhat that produced by the nitrophenols (35). (One cannot help but draw the analogy between the current use of DDT and the short-lived mania for dinitrophenol a decade ago. This substance too, on the basis of an impressive toxicologic investigation, was thought safe in limited dosage for human beings — until they began to develop cataract and other serious ill effects from its use). Riker and his collaborators (35) further pointed out the resemblance between some of the effects of DDT produced in animals and those of paraphenylenediamine and hydroquinone. No one nowa-

† One patient in the series reported in this paper, had been heavily exposed to DDT spray without apparent ill effect. A year later he was again exposed and promptly collapsed; he had nausea, vomiting, diarrhea, extreme muscular weakness, pain and aching in the limbs, etc. See also references 31 and 32.

days would even consider indiscriminate exposure of the public to these compounds.

An example of current impressions about the safety of DDT for the public appears in a recent issue of LIFE magazine. In a series of pictures DDT aerosols are shown being applied from an airplane and by ground equipment to the grounds of a resort, the inside of a cowbarn and a house and the like. Adults, children and cattle are shown engulfed by the aerosol, which is implied to be harmless, "The fog covers everything with a submicroscopic and stainless film of poison, lethal to insects but harmless to humans, animals and food." Indeed, a young lady is shown holding a sandwich and drinking a beverage in the midst of the aerosol cloud. Says LIFE "Unlike dust or spray the fog will not contaminate food."

In the course of inquiries made of numerous individuals, once DDT poisoning as a clue to the "virus X" syndrome became apparent, I was amazed to find that many persons use DDT solutions as freely as they would a detergent, and with no safeguards whatever to avoid personal contact. Additionally, serious illness and death in animals exposed to DDT, in every case attributed to infection, came to light. Two dogs dusted with DDT acquired severe "distemper" and had to be destroyed. In an apartment, within a few hours after the closets and their contents were intensively sprayed with DDT, a cocker spaniel began to vomit, developed convulsions and died the next day. Three young dogs kept in a kennel sprayed daily with DDT developed "distemper" and died, at a time when there had been no other cases of distemper among dogs in the neighborhood. (Hill and Robinson (3) reported death of two bull terriers sprayed with DDT). A siamese cat dusted with DDT developed convulsions in a few hours and died some days later with paralysis of the hind limbs. On a cattle ranch in which the animals were heavily dusted with DDT, a mysterious affection caused numerous deaths in these animals from a hemorrhagic, perforating enteritis, never before observed. In a midwestern farming community, numerous cases of an intractable hemorrhagic diarrhea ("black scours") have been occurring among cattle dusted or sprayed with DDT, kept in barns sprayed with this agent or fed with contaminated fodder. Many of these cattle have died. The "X disease" which ("although it started only recently") is reported to have caused serious losses among cattle in at least 26 states, bears a remarkable resemblance to the known effects of DDT poisoning.‡

There is no question that the DDT problem requires intensive further investigation. In the meantime, public health officials might well consider seriously the joint statement issued in 1945 by the U. S. Army and U. S. Public Health Service (37), While this statement is concerned primarily with mosquito control and does not adequately cover the possibility of toxic effects to human beings and domestic animals, the cautions there advised are relevant to all the uses of DDT:

"Successful use of the new insecticide DDT to combat insect-borne disease among our troops overseas has brought sudden renown and notoriety to this potent war-developed insect killer. Dramatic results of its large-scale use to control epidemics, and the spraying of DDT from aircraft, have fired public imagination and fostered the hasty conclusion that DDT is a complete solution to all our insect-borne disease problems. However, it must be remembered that DDT distributed over the countryside not only wipes out malaria-carrying mosquitoes but also may kill other insects, many of which are beneficial. Much still must be learned about the effect of DDT on the balance of nature, important to agriculture and wildlife, before general outdoor application of DDT can be safely employed in this country. It may be necessary to ignore these considerations in war areas where the health of our fighting men is at stake, but in the United States such considerations cannot be neglected. Extensive investigations are now being carried out by authorized agencies to determine the usefulness and possible hazards in the large-scale dissemination of DDT. Until more information has been obtained from such investigations and until it has been evaluated by all interested parties, plans to employ DDT indiscriminately for outdoor area control of insect disease vectors in this country are not to be encouraged."

SUMMARY

Evidence is presented that the new syndrome widely prevalent in the United States for more than two years and attributed to infection with a hypothetical "virus X," is in reality due to DDT poisoning.

† "X disease" of cattle is described as follows (Prairie Farmer 120:31, Aug. 28, 1948): "Young animals are most susceptible. Severely affected animals usually die. Pregnant animals frequently abort. It lasts from several weeks to about three months. Four to eight per cent of affected cattle die. Symptoms include a watery discharge from the eyes and nose, failing appetite, loss of condition, depression, and a gradual thickening of the skin. Sometimes diarrhea occurs in the late stages." Later reports indicate the incidence to be 31 per cent and the mortality 59 per cent.

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Surgical Considerations of Choledocholithiasis

By

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SURGICAL EXPLORATION of the common bile duct has increased in frequency during the past ten years. There are several reasons for this. First, patients with cholelithiasis and without jaundice may have stones in the common duct (1). Such calculi may be first observed at operation. Second, there is a lower morbidity today in patients operated upon for common duct obstruction (2). This is due almost entirely to improved preparation of each patient and the realization by the gastroenterologist that cholelithiasis requires surgical therapy. Third, technical advance has placed tumors of the pancreas and in the region of the papilla of the bile duct within the scope of surgical attack (3).

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DIAGNOSIS

Early diagnosis of common duct disease is a most important aspect in surgical therapy. It may be difficult to differentiate intra- from extra-hepatic jaundice, particularly if the icterus is of several weeks duration (1). It is of significance that jaundice may be found in fifty per cent of patients with common duct stone. On the other hand, exploration of the common duct reveals that fifty per cent of jaundiced patients have a stone as the cause for the jaundice (4).

In addition, a tumor less than one centimeter in diameter which is located near the termination of

the common duct may produce massive metastases before it obstructs the common bile duct (5).

Damage to the liver or pancreas may be the first indication of biliary tract disease. In this regard a doubtful diagnosis may be clarified by laboratory studies of the duodenal drainage to indicate the character of bile and pancreatic secretions and of the feces to determine the efficiency of the pancreatic enzymes. In the absence of a clear clinical picture, radiographic study of the stomach and duodenum as well as the cholecystogram becomes a most reliable diagnostic aid.

In clinical diagnosis of common bile duct disease, calculi are to be differentiated from carcinoma of the pancreas and biliary passages, from cholangitis, and from disease which is extrinsic to the bile ducts. In cases with neoplasm, a mass is frequently palpable, although jaundice following a previous resection for carcinoma of the bowel can be due to choledocholithiasis as well as to metastatic lymphadenopathy. When cholangitis alone is present, pain is usually absent. The usual course of cholangitis, however, is that it ordinarily occurs in the event of an obstruction to the biliary flow which is complicated by a chronic infection. The obstruction, per se, may be painful. When extrinsic pressure is exerted on the bile ducts and when the gall bladder is not the primary site of disease, distention of the bile ducts and gall bladder may be enormous, and under those conditions the gall bladder may be easily palpable. Extrinsic pressure on the bile passages may be of malignant origin, but is also associated with the contraction from scarring associated with a chronic duodenal ulcer, or by pressure from a diverticulum of the duodenum, or secondary to a chronic sclerosing pancreatitis (6).

The common duct presents a difficult problem at the time of operation. In approximately two-thirds of cases, the pancreatic portion of the common bile duct is not directly palpable. A probe which is passed into the common duct may slip by a calculus. A catheter can be placed into the duct and may appear to enter the duodenum, whereas it is only pushing the papillary portion of the common bile duct into the lumen of the duodenal canal. Fluid may be washed into a catheter or directly into the duct and pass into the duodenum in spite of organic disease existing in the common duct. Under some circumstances, the technical disadvantages of direct cholangiography at the time of operation, outweigh its usefulness.

PATHOLOGICAL CONSIDERATIONS

The primary function of the biliary tract is to act as a carrier. Its most critical area is at its termination within the duodenum. The anatomical and pathological characteristics of the papilla are, hence, of great importance. However, our standard texts in anatomy, medicine and surgery retain the basic observations made forty years ago and before (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17). More recent observations providing an improved understanding of the anatomy and physiology of the ducts have ap-

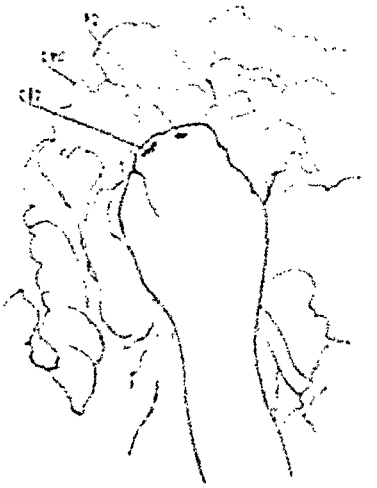


Fig. 1. — The pancreatic duct joins the common bile duct just outside the duodenal wall. Distal to this junction there is a swelling in the appearance of the common bile duct tissues. However, within this swelling, the lumen of the common bile duct is distinct from that of the pancreatic duct, and they each have separate orifices.
PD: orifice of pancreatic duct
DMU: duodenal mucosa
CBD: orifice of common bile duct

space, which is implied by the term "ampulla." It is a mass, wherein the wall of the common duct increases in size due to fibrous and muscular tissues which aggregate to form a so-called "sphincter of Oddi" (24) (Fig. 2). This can be demonstrated on any cholangiogram wherein the lumen of the common

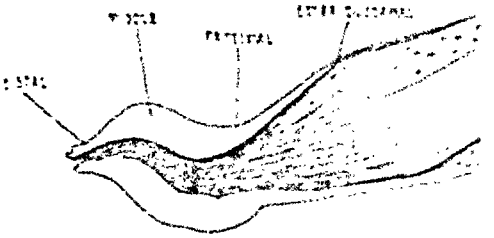


Fig. 2. — The major divisions of the termination of the common bile duct are indicated as (1) extraduodenal and (2) transduodenal, composed of (a) proximal, (b) middle and (c) distal thirds. The lumen of the common bile duct decreases in diameter. The apparent enlargement in the tissues of the common duct is not a space, but represents a mass of muscular tissue.

bile duct is seen to decrease rapidly in diameter and to terminate as a filamentous canal (Fig. 3). Normally, there is no ampulla.



Fig. 3. — Normal cholangiogram: diodrast enters the duodenum through the "T" tube without delay. There is a medial convexity and the lumen tapers slowly to end in an "S" shaped curve with a filamentous channel and empties into the descending portion of the duodenum at the level of the transverse process of the third lumbar vertebra.

In addition, the course of the common bile duct in its transduodenal segment, is that of a flat "S" shaped curve. The passage of any large metal instrument (such as the Bakes dilator) is known to be followed by a choledocho-duodenal fistula and by an edema which can produce transient or permanent obstruction to the common bile duct (25). Hence, only a flexible instrument smaller than three millimeters in diameter, such as an ureteral catheter should be passed into or through the papilla.

Stones which impact within the common bile duct are usually found at the termination of the extra-duodenal segment of the common bile duct. These may be asymptomatic. However, continued lodgement at the proximal portion of the papilla can produce diverticula of the common duct (26), or a choledocho-pancreatic or choledochoduodenal fistula (27) and can be further complicated by hepatitis, cholangitis, pancreatitis and complete biliary tract obstruction (28).

INDICATIONS FOR CHOLEDOCHOTOMY

The surgical indications for exploration of the common bile duct, most frequently, are a corollary to examination of the gall bladder. The patient with cholelithiasis and jaundice should be treated by surgery. If the cholecystogram reveals stones in the gall bladder in the absence of jaundice the patient should also be prepared for cholecystectomy. Usually, if sufficient indication for the cholecystography has been presented, that patient's symptoms may respond to cholecystectomy for cholelithiasis. There is more reason than pure symptomatic relief to indicate cholecystectomy in calculous disease of the gall bladder. Prophylaxis regarding eventual carcinoma of the gall bladder is to be considered, since it has been repeatedly demonstrated that at least four per cent of patients with cholecystitis have carcinoma of the gall bladder and that it is a rare case of carcinoma of the gall bladder which exists in the absence of cholelithiasis. The gastroenterologist no longer procrastinates in referring the patient with chronic calculous cholecystitis for surgical therapy.

Should there be no calculi revealed on cholecystography, the clinical problem depends upon the extent of damage to gall bladder function, the qualitative analysis of symptomatic distress, and the strong suspicion regarding possible pancreatic tumor.

The final decision for opening and exploring the common bile duct has to be made at the operating table. There are six major groups of patients in whom this procedure is indicated.

1. Cholelithiasis with a stone palpable in the common duct.

2. Cholelithiasis, when the common duct is thickened, and dilated or distended to one centimeter or more in diameter.

3. Small stones, or a friable large stone in the gall bladder, particularly if the cystic duct be patent. In such cases, a past history of jaundice is an absolute indication for exploring the common duct.

4. The gall bladder may or may not have stones, but the pancreas is edematous or indurated and evidence of fat necrosis may be found.

5. No stones in the gall bladder but symptoms which point towards the biliary tract.

6. Suspicion: abnormal anatomical findings, a palpable mass in or near the biliary tract or obstructive jaundice without obvious cause.

The clinical indications for exploration of the common bile duct, then, are obstructive jaundice, cholelithiasis and certain of its complications, and tumor suspected to be located in the biliary passages or adjacent tissues. One additional complex can be considered; the post-cholecystectomy syndrome. Briefly, this syndrome can be due to traumatic or inflammatory stricture of the common duct, to pancreatitis, hepatitis, or residual calculi in the common duct, or from a neuroma or scar in the stump of the cystic duct, or postoperative adhesions, or may be secondary to disease in the pancreas, stomach or duodenum. Frequently, a surgical approach to the post-cholecystectomy syndrome is successful.

PREOPERATIVE MANAGEMENT

The preparation of the patient for operation on the biliary tract should include an investigation of the cardiovascular system. Other causes for abdominal distress must be evaluated, including disease of the central nervous system (29). This study is not only for differential diagnosis, but also to aid in the selection of the anesthetic agent.

Liver function tests are essential. Icterus index, prothrombin time and serum proteins (including albumen to globulin ratio) may be sufficient. In some cases of prolonged illness, it is wise to study the bromsulfalein excretion or hippuric acid conjugation and to determine the ratio of cholesterol to its ester fraction. Laboratory tests are not infallibile. Clinical judgment and adequate management will provide best assurance for a successful surgical result.

If the patient does not present evidence of liver damage or biliary tract infection, preoperative management may be completed with the patient under medical care at home. In such cases, over a ten to fourteen day period, oral fluids to two thousand cubic centimeters, sixty to seventy-five grams of carbohydrate and one hundred grams of protein are given daily. Vitamin K, amino acid concentrates and other medication may be indicated. This group of patients may be admitted to the hospital twenty-four to forty-eight hours prior to surgery.

The patient who has liver damage, cholangitis, hepatitis, or jaundice should be hospitalized for five to seven days after the two week preparatory period just described. During the preoperative period of hospitalization, the gastrointestinal tract is placed at rest, protein and carbohydrate are administered parenterally and, if indicated, choline, methionine, vitamins B and C, and whole blood transfusions are given.

POSTOPERATIVE CARE

During the first forty-eight hours, oral intake is limited postoperatively. Fluids are given parenterally. To avoid shock, and hepatic insufficiency, the most favorable anesthetic agent had been selected, and when needed, oxygen and blood utilized.

In most cases early ambulation is effective and muscular exercises, deep inhalations and coughing are well tolerated by the patient. Some patients because of cardiac complications require restrictions on their physical activity. In these, a prophylactic vein ligation may be done, or dicoumarol administered after the second postoperative day. Patients who have active or subsiding inflammation of the biliary tract are given an appropriate antibiotic agent such as penicillin, sulfadiazine or streptomycin. Vitamins, B, C and K are given in ample dosage, most particulary if the patient was jaundiced.

When the common duct is opened, a "T" tube or catheter is placed in situ. In most cases, gravity drainage of bile through the tube is the method of choice. In some cases, if there has been long standing obstruction to the biliary tract, a slow decompression of the biliary tract is beneficial. Patients who present spasm of the terminal segment of the common bile duct may require gradually increasing pressure within the common duct.

In patients with a choledochostomy, a cholangiogram is done after the seventh post-operative day. Radiographic findings are checked against measurements of the duct volume, determinations of intracholedochal pressures, and an estimation of the rate of flow from the duct.

Under certain circumstances the tube may remain in the common duct for many months. This is particularly indicated where there is residual dilatation of the bile passages. Ordinarily, when the cholangiogram and the pressure/volume studies are normal, the "T" tube is removed from the common duct on the ninth or tenth postoperative day.

Three-month and yearly follow-up examinations are considered essential to the management of the patient who has been treated surgically because of disease of the common bile duct.

CONCLUSION

Patients with biliary tract disease should be prepared for possible operation on the common bile duct. There is little increase in morbidity when the common bile duct is examined directly in patients with obstructive jaundice, cholelithiasis and its complications, suspected tumor and in the post-cholecystectomy syndrome.

Improved results in patients with common bile duct disease have been due as much to preoperative diagnosis and management by the family physician and the non-procrastinating gastroenterologist as to improved knowledge and surgical skill.

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Effect of Acetyl Salicylic Acid on the Gastric Mucosa of the Shay Rat *

By

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THE EFFECT OF ASPIRIN on the anatomy and physiology of the stomach has been investigated by many workers (1). In 1947, Clark and Adams (2), reported that there was no increase in gastric secretion in Cope pouch dogs receiving oral administration of 95 mgs. of acetyl salicylate per kg. per day. However, if large doses (200 mgs. per kg. per day) were given, sufficient to cause anorexia, nausea, vomiting and gastric irritation, an increase in gastric secretion did take place.

Caravati (3), performed a series of gastroscopic examinations on twenty patients kept on salicylate for twenty days. He found no gastritis in nineteen of these patients. If nausea or vomiting occurred, it could be correlated with high salicylate levels in the blood, even though the gastric juice contained little aspirin. The distress after large doses of this drug is attributed to the effect of salicylate on brain centers rather than on the gastric mucosa.

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The gastroscopic studies of Paul (4), on a large number of patients receiving aspirin in doses as high as 80 grains per day had disclosed no demonstrable hyperemia nor damage to the gastric mucosa. Even if ingested over long periods of time, aspirin was not found to produce chronic gastritis. However, inasmuch as 5% of the patients complained of epigastric distress following the ingestion of aspirin, Paul attributed these symptoms to pylorospasm and increased acid production rather than to gastric lesions.

To corroborate this theory, it was decided to study the effect of high doses of aspirin on the gastric mucosa of a large number of animals. In our work, a modification of the Shay technique (5, 6), for producing gastric lesions in rats was employed. The ulceration in the gastric mucosa which resulted six hours after ligation of the pylorus in a group of rats receiving two mls. of either 0.01 N HCl, distilled water, or 0.9% NaCl orally, was compared with the mucosal damage observed in similarly operated rats receiving 2 1/2 grains of aspirin in a two ml. volume of one of the above mentioned carriers. The volume of the gastric contents was measured and the pH, free and total acidity were determined. Attempts were made to

correlate severity of mucosal lesions with free and total acidity, pH, and rate of gastric secretion.

GENERAL PROCEDURE

Stock rats of both sexes ranging in weight between 120 and 385 grams and previously maintained on a balanced ration were fasted for 72 hours, water being freely available until one hour prior to the operation. A midline abdominal incision extending from the xiphoid process to approximately one inch below this point was made, under light ether anesthesia. A heavy cotton thread ligature was placed around the pylorus with a minimum of disturbance to the surrounding viscera and without touching the stomach under any circumstances. The incision was closed at once. A fine rubber catheter attached to a syringe was passed into the stomach and two ml. volumes of the substances under study were administered. Recovery from the operative procedure was prompt and satisfactory.

At the end of six hours, the animals were sacrificed by a sharp blow on the head and the stomachs were excised after clamping off the esophagus with a hemostat. The gastric contents were poured into a graduated centrifuge tube and were measured after centrifuging off the solids. The empty stomachs were opened along the greater curvature and the interior was examined for lesions, using a dissecting microscope. Specimens contaminated with blood or containing food were discarded. All total volumes were corrected for the two ml. of substance originally administered and for the solids found. The free and total acidity of the gastric juice were determined by titrating one ml. volumes with 0.02 N NaOH using Töpfer's solution and phenolphthalein, respectively. *Free and total acidity are expressed as milliequivalents of HCl per 100 ml. gastric juice.*

Our findings are summarized in Table I which covers observations on a total of 66 rats, of which 31 served as controls and 35 received aspirin. To uniformly describe the severity of the gastric ulceration the following integer and decimal notation has been adopted:

Designation	Pathology
1.0	Hemorrhage of vessels in gastric mucosa and incipient ulceration
2.0	Many small punctate ulcers
3.0	Several eroded ulcer areas
4.0	Deeply pitted areas of ulceration with necrosis
5.0	Perforation of gastric wall
0.1	Ischemia localized in rumen
0.2	Hyperemia in rumen
0.3	Petechiae and vasodilatation in body
0.4	Erosion and thinning of wall of rumen which becomes more transparent than usual
0.5	Ischemia in body

TABLE I

Changes in the Stomach of Control Rats

No.	Treatment	Gastric Pathology	Gastric Juice Analysis: Rate of Secretion	Free Acidity	Total Acidity	pH
			ml./hr./100 gm.	milli-eq. HCl/100 ml.		
1	2 cc. 0.01 N HCl	3.5	0.32	19.0	52.0	2.9
2	2 cc. 0.01 N HCl	4.0	0.48	42.0	72.0	2.2
3	2 cc. 0.01 N HCl	4.0	0.31	22.2	50.0	2.4
4	2 cc. 0.01 N HCl	4.0	0.62	29.8	78.2	2.6
5	2 cc. Distilled H_2O	1.0	0.27	51.6	100.8	2.7
6	2 cc. Distilled H_2O	2.0	0.00			
7	2 cc. Distilled H_2O	3.0	0.56	46.0	91.8	2.3
8	2 cc. 0.9% NaCl	4.5	0.45	72.2	82.8	2.1
9	2 cc. 0.9% NaCl	1.2	0.15	17.0	46.0	2.8
10	2 cc. 0.9% NaCl	4.3	0.83	94.2	144.2	2.0
11	2 cc. 0.9% NaCl	3.5	0.30	47.6	90.0	2.7
12	2 cc. 0.9% NaCl	2.1	0.38	12.0	88.0	3.1
13	2 cc. 0.9% NaCl	2.3	0.32	10.0	96.0	3.2
14	2 cc. 0.9% NaCl	4.0	0.57	40.0	104.0	2.1
15	2 cc. 0.9% NaCl	4.0	0.42	56.0	96.0	2.1
16	2 cc. 0.9% NaCl	4.3	0.72	44.0	92.0	1.8
17	2 cc. 0.9% NaCl	4.3	0.48	25.0	83.0	1.4
18	2 cc. 0.9% NaCl	0.0	0.70	47.8	116.0	1.2
19	2 cc. 0.9% NaCl	4.3	0.00			
20	2 cc. 0.9% NaCl	4.3	0.72	21.2	64.4	1.5
21	2 cc. 0.9% NaCl	4.3	0.76	40.0	82.0	1.2
22	2 cc. 0.9% NaCl	5.0	0.68	52.8	109.6	1.5
23	2 cc. 0.9% NaCl	4.2	0.34	23.2	81.2	2.8
24	2 cc. 0.9% NaCl	4.0	0.60	12.0	59.6	3.0
25	2 cc. 0.9% NaCl	5.0	0.59	43.0	73.0	1.7
26	2 cc. 0.9% NaCl	1.2	0.31	19.0	39.0	2.9
27	2 cc. 0.9% NaCl	4.2	0.29	0.0	48.0	3.9
28	2 cc. 0.9% NaCl	5.0	0.23	11.0	87.0	3.1
29	2 cc. 0.9% NaCl	4.2	0.63	15.0	68.0	2.6
30	2 cc. 0.9% NaCl	4.0				
31	2 cc. 0.9% NaCl	4.3				
	Average		0.40			

Table I Continued

Changes in the Stomach of Rats Receiving Aspirin

No.	Treatment	Gastric Pathology	Gastric Juice Analysis, Rate of Secretion	Free Acidity	Total Acidity	pH
			ml./hr./100.gm.	milli-eq. HCl/100		ml.
1	2 1/2 grains aspirin	0.3	0.35	0.0	133.8	3.8
2	2 1/2 grains aspirin	0.2	0.69	0.0	211.2	3.3
3	2 1/2 grains aspirin	0.2	0.25	0.0	105.6	3.8
4	2 1/2 grains aspirin	2.2	0.51	0.0	102.8	3.1
5	2 1/2 grains aspirin	1.2	0.40	0.0	128.6	3.9
6	2 1/2 grains aspirin	2.3	0.76	0.1	129.2	3.1
7	2 1/2 grains aspirin	0.2	0.50	0.0	102.2	3.3
8	2 1/2 grains aspirin	2.3	0.09	0.0	119.4	3.6
9	2 1/2 grains aspirin	2.3	0.45	0.0	121.8	3.3
10	2 1/2 grains aspirin	2.3	0.33	0.0	192.4	4.0
11	2 1/2 grains aspirin	1.2	0.22	0.0	76.0	3.4
12	2 1/2 grains aspirin	1.2	0.22	0.0	58.0	3.4
13	2 1/2 grains aspirin	3.2	0.14	0.0	64.6	3.5
14	2 1/2 grains aspirin	4.2	0.15	0.0	44.6	3.7
15	2 1/2 grains aspirin	1.2	0.19	0.0	62.0	3.2
16	2 1/2 grains aspirin	0.2	0.15	0.0	64.5	3.5
17	2 1/2 grains aspirin	0.2	0.24	0.0	68.4	3.4
18	2 1/2 grains aspirin	1.2	0.21	0.0	66.2	3.4
19	2 1/2 grains aspirin	0.3	0.54	0.0	49.6	3.5
20	2 1/2 grains aspirin	0.3	0.29	0.0	60.0	3.7
21	2 1/2 grains aspirin	0.0				
22	2 1/2 grains aspirin	0.2				
23	2 1/2 grains aspirin	0.0				
24	2 1/2 grains aspirin	1.0				
25	2 1/2 grains aspirin	4.0				
26	2 1/2 grains aspirin	0.3	0.09	0.0	22.4	4.4
27	2 1/2 grains aspirin	0.2	0.24	0.0	15.0	5.6
28	2 1/2 grains aspirin	0.2	0.28	0.0	23.0	5.1
29	2 1/2 grains aspirin	1.2	0.34	0.0	24.8	5.1
30	2 1/2 grains aspirin	0.0	0.28	0.0	13.8	5.7
31	2 1/2 grains aspirin	0.2	0.23	0.0	19.8	5.2
32	2 1/2 grains aspirin	0.0	0.76	0.0	20.4	5.2
33	2 1/2 grains aspirin	0.0	0.27	0.0	29.4	5.0
34	2 1/2 grains aspirin	0.0	0.30	0.0	29.4	5.0
35	2 1/2 grains aspirin	0.5	0.39	0.0	77.6	4.8
	Average		0.32			

The integer describes the severity of the lesions; the larger the number, the greater the damage. The decimal, on the other hand, merely indicates our general observations regarding the state of the mucosa and no attempt has been made to correlate the degree of damage with the magnitude of the decimal.

In table II is given a summary of gastric pathology by groups:

It is evident that 30 out of 31 control rats showed gastric lesions of varying extent, while only 15 out of 35 rats receiving aspirin had any grossly visible ulceration. Moreover, 20 of the rats receiving aspirin showed no ulceration at all. These findings seem to be in close agreement with those of Pauls, Wick and MacKay (7), who reported recently that when the salts of o-hydroxybenzoic acid were administered to rats with ligated pylorus, the formation of ulcers was

TABLE II

No. of rats	Treatment	Pathological Index 0	1	2	3	4	5
4	2 ml. 0.01 N HCl				1	3	
3	2 ml. distilled water		1	1	1		
24	2 ml. 0.9% NaCl	1	2	2	1	15	3
35	2 1/2 grains aspirin in 2 ml. H_2O	20	7	5	1	2	

prevented. They found that the most effective route of administration is by vein, but the protective action results also after oral or intraperitoneal administration. The meta and para sodium salts are less active. Acetyl salicylic acid afforded almost as much protection as the ortho-hydroxybenzoic acid. The only difference between our technique and the one employed by Pauls and co-workers was that their animals were fasted 48 hours instead of 72 and they sacrificed their rats nine hours after pyloric ligation instead of after six as we did.

Analysis of our data shows that the gastric contents of the rats receiving aspirin had almost no free acidity and that the pH was considerably higher than in the

case of the control animals. Rates of secretion in both the control and experimental groups show a range of values which has almost exactly the same upper and lower limits. The average value for rate of secretion was calculated for both control and experimental groups, and it was found that the experimental average was 20% lower than the control average. Aspirin thus appears to have an anti-secretory effect under the experimental conditions we have employed. Whether the decrease in free acidity and in the rate of secretion is responsible for the lessened incidence of ulceration in the rats receiving aspirin awaits further study using larger numbers of animals, inasmuch as these observations are less evident on an individual than on a group or statistical basis.

CONCLUSIONS

1. While 30 out of 31 rats receiving oral administration of two ml. volumes of 0.01 N HCl, distilled water, or 0.9% NaCl showed gastric lesions six hours after pyloric ligation, only 15 out of 35 animals receiving 2 1/2 grains of aspirin showed evidence of gastric damage.

2. The rats receiving aspirin showed a lower rate of secretion of gastric juice and had almost no free acidity in the gastric content.

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Bleeding Per-Ano

BY

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THE PRESENT RADIO AND NEWSPAPER PUBLICITY being given the subject of cancer has caused many more patients with bleeding per-ano to seek diagnosis than of yore.

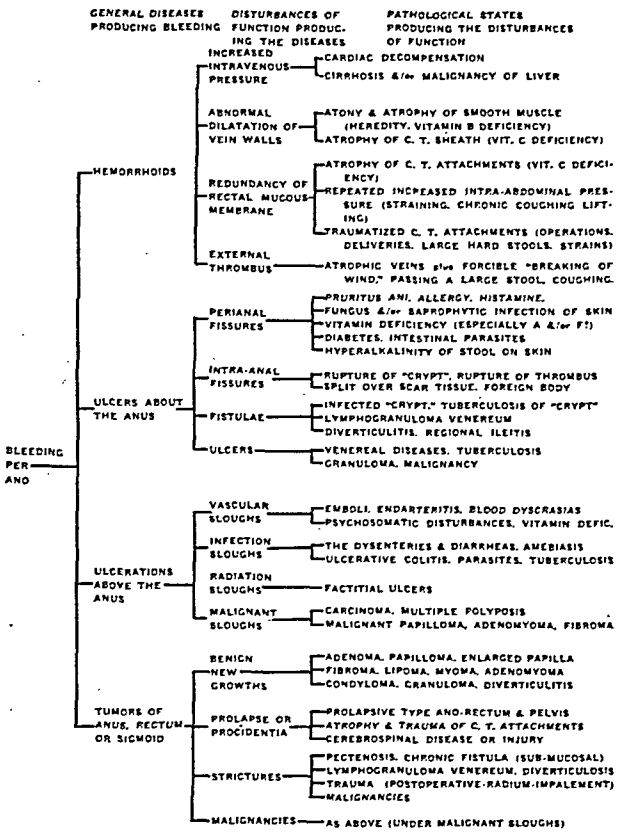
In the past, the discovery of some blood following a bowel movement usually suggested the presence of some hemorrhoids and the advice of a friendly druggist was solicited. Now, however, with the popular and widespread emphasis on the possibility of malignancy being present with any sign of blood from an orifice, the hideous spectre of cancer is evoked in the layman's mind and he immediately hastens over to his doctor or to the proctologist fully convinced that "he is not long for this world." Yet it is a fact that nearly every proctological ailment is accompanied by bleeding either routinely or on occasion and as will be seen there are a great number of such ailments. Therefore consideration of this subject practically constitutes a review of the whole of proctology. But the latter is a specialized branch of medicine which is seldom taught to undergraduates and consequently has become a popular post-graduate or extension course. Some years ago, in order to simplify and condense this subject of bleeding per-ano, we compiled the accompanying table (Table 1). Its use soon revealed it to be an outline of Proctology brought together under an interesting heading. Consequently, it has been employed as such ever since.

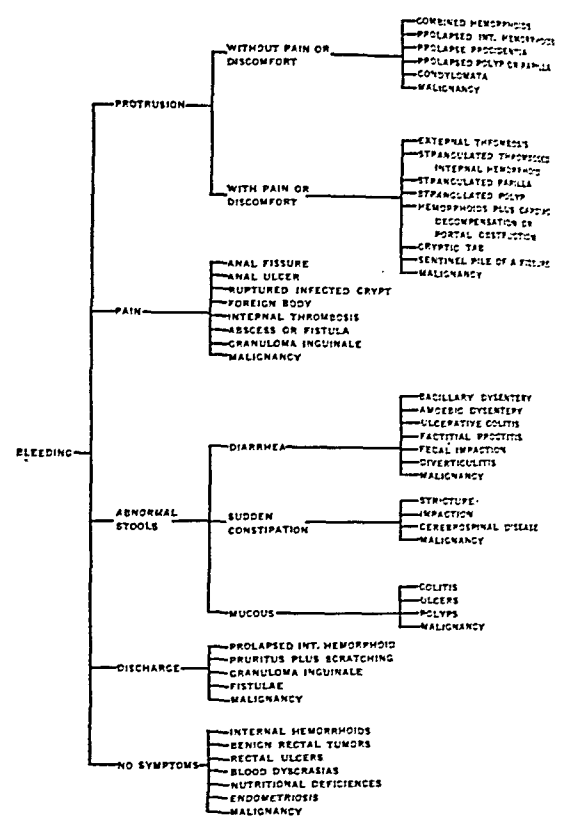
An examination of this table will show that bleeding per-ano (and, concurrently, the subject of Proctology) can be divided into four major components the latter being the four general disorders which produce bleeding in the sigmoid, rectum and anus (second column). Each of these four general disorders are brought about by certain disturbances of function of the part involved as enumerated in the third column of the table while these disturbances of function are, in turn, found to be the result of certain pathological states as listed in the last column.

It will be seen, therefore, that there are about a hundred ailments, disturbances of function or pathological entities to be taken into consideration whenever a patient complains of this type of bleeding. It might seem that this would be very confusing and require an exacting search before the correct diagnosis could be made. However, experience has shown that a pretty good approach has been achieved

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by the time the history has been taken, while anoscopic and sigmoidoscopic examinations leave a very small residue of conditions requiring X-ray, laboratory and special investigations. (We are not concerned here with tarry stools indicating partially digested hemorrhage from a source higher up, although very occasionally such bleeding may be so profuse and the rate of peristalsis so rapid that it does appear as fresh blood on defecation).

Duration, Amount and Type of Bleeding

In taking the history especial emphasis should be placed on the duration, the amount and the type of bleeding and whether it is accompanied by other symptoms. As to *duration* — bleeding off and on for a number of years in a young person hardly indicates malignancy although, as will be seen, the latter diagnosis must always be ruled out by further examination unless the symptom is quickly and definitely obliterated by the discovery and treatment of some other condition. On the other hand, bleeding of a few weeks' or months' duration and of a persistent nature in a person of middle age or beyond requires prompt sigmoidoscopic and X-ray examinations with malignancy or ulcerative colitis as definite possibilities.

The *type* and *amount* of bleeding is often overlooked. A stain on the paper following an evacuation is usually indicative of some minor condition at the anal verge while active bleeding into the water as the patient remains sitting on the bowl following a bowel movement is quite suggestive of a ruptured, prolapsing internal hemorrhoid. Clots mixed with or on the stool usually mean trouble higher up; for instance, a streak of red blood on the side of the movement is very suggestive of a polyp, while dark clots embodied within the waste matter intimates malignancy well *up* in the sigmoid or lower colon. Explosive bleeding with mucous often signifies the existence of a well advanced entity well *down* in the rectum or lower sigmoid, either an ulcerative colitis or a malignancy.

Other Proctologic Symptoms Plus Bleeding

Furthermore, if, in addition to the information obtained as above outlined concerning the type, duration and amount of bleeding, one or more other proctologic symptoms are found to accompany the bleeding-per-ano, some very close snap diagnoses can be made even prior to examination. For instance, bleeding of a few days duration consisting of a stain on the paper but accompanied by exquisite *pain* at time of and following a bowel movement portrays a picture almost pathognomonic of a fissure-in-ano at the posterior commissure. (Anterior fissures often have bleeding as their *only* symptom). Again, dark, clotted blood mixed with or on the stool plus a *change in bowel habit* points very strongly toward malignancy at or above the recto-sigmoid junction. On the other hand, *diarrhea* of long duration associated with the subsequent appearance of blood suggests an ulcerative colitis. The various possibilities will be recognized when Table II is examined. Bleeding plus *tenesmus* (not mentioned in the table) calls for careful examination of the lower rectum with

malignancy, proctitis and lymphomata, as possibilities.

However, in taking into consideration these other proctologic symptoms it is also well to obtain in turn *their duration,* a description of the *character of their onset* and information concerning any *periodicity of recurrence.* In Table II. will be found only the simple symptom bleeding-per-ano accompanied by other simple but important proctologic symptoms with the resulting possible diagnoses when the two are considered in conjunction. But, if to bleeding-per-ano is added protrusion and pain, it makes a difference whether the protrusion is of short or long duration and whether the pain is constant or disappears only to return at the time of a bowel movement — short duration of a painful protrusion with bleeding would indicate a sloughing external thrombosis or the sudden prolapse and semistrangulation of a polypoid tumor, while the same symptoms with a longer duration would not do so. Again, if with bleeding-per-ano, constipation is had, it makes a difference whether the constipation came on recently or had been present for years. The character of the onset of some of these other symptoms is often illuminating. Excruciating pain appearing suddenly with a bowel movement and remaining constant suggests the possibility of a foreign body or a fissure in the anus while a soreness developing gradually into pain probably means an abscess. On the other hand, if pain appears an hour or two after forceably breaking wind, we are presented with the probability that an external thrombosis was produced by the hapless incident. Periodic diarrhea having its onset in a prolonged acute, feverish attack of "dysentery" has been found to signify acquired allergy to some one food product, usually milk (12). A gradual onset of diarrhea has no such signification.

REFLEX SYMPTOMS IN PROCTOLOGY

Before leaving the matter of symptomatology it is well to remember that reflex symptoms can occur in other organs from pathology located in the anus or rectum while, conversely, symptoms in the latter regions often accompany trouble in some neighboring organ. For instance, an inability to void accompanying an unlocalized discomfort in the perineum is often the first indication that a high antero-lateral perirectal abscess is developing. A diagnosis of coccygodynia should never be made until careful search for the presence of a recto-sigmoidal malignancy has been carried out. Constipation often has been found by proctologists (1, 2, 3) to disappear on eradication of a chronic fissure or a subacutely infected anal duct at the posterior commissure. In fact a whole system of local and remote reflex and referred symptoms and abnormal functions has been built up on the basis of neural excitation by pathological states in the anus (13). Strangely enough, sometimes, this turns out to be true. On the other hand, a distended prostate, an endometriosis in the recto-vaginal septum, a tumor of the adnexa or a uterus so retroverted that its fundus lies on the anal musculature are often only discovered because they gave rise to symptoms in the anus or rectum.

PROCTOLOGIC EXAMINATION

The proctologic examination should be thoroughly and systematically carried out. It involves several distinct steps performed in the following order:

1. History (including a dietary history)
2. Abdominal examination when the history indicates the need for it.
3. Visual peri-anal examination.
4. Digital examination.
5. Anoscopic examination.
6. Sigmoidoscopic examination.
7. Laboratory examination of biopsies, cultures, mucous, scrapings or feces taken from the rectum or sigmoid through the sigmoidoscope.
8. Barium Enema. Contrast Air Enema.
9. The Bolen Blood Pattern (7).
10. Examination of stools:
 a. Routine exam. for occult blood, ova, etc.
 b. Exam. of several warm stools for amoebae.
 c. Exam. of the second stool after a dose of mag. sulph. for amoebae.
 d. Exam. for the percentage of pathological streptococci in the stools (in colitis)
11. Special tests such as the Frie test, agglutination tests, vaginal examination, examination of the blood, etc.
12. Diagnosis by therapeusis.

The reason why the investigation should be carried out so systematically is that even the most experienced diagnostician will sometimes miss something in one section of the examination but will probably not miss it in two sections. It is well known that there is a blind spot in the recto-sigmoid by roentgen examination requiring sigmoidoscopic exploration before malignancy is ruled out. A polyp placed anteriorly in the lower rectum is easily missed on digital examination but will most probably be picked up either on anoscopic or sigmoidoscopic examination or vice versa. Furthermore, it may require the positive or negative evidence obtained from several sections of the examination to establish a diagnosis. The finding of some deep crypts means nothing without the presence of a pecten band and a history of intolerable burning exacerbated by periods of pain and soreness (5). Or, the finding of the typical signs of an irritable colon by sigmoidoscopic examination (4) needs confirmation in a well taken history, an abdominal examination, a Barium enema, psychiatric study (6) and even by therapeutic diagnosis. On the other hand, a diagnosis of simple mucous colitis should not be made by deduction alone (after seeing specks of blood and mucous on a stool)

have to be made by means of therapeutic elimination and deduction, i. e. sclerosing the hemorrhoidal area, treating as for mucous colitis (so-called), correcting blood and vascular conditions, giving supplementary vitamins and in therapeutic dosage, even giving a course of amoebicides in suspected cases.

SUMMARY

Bleeding per-ano has long been conceived as originating in either hemorrhoids or cancer. However, it is shown that bleeding per-ano may accompany about a hundred ailments, disturbances of function or pathological entities. Consideration of this subject practically constitutes a review of the whole of proctology and might appear to be confusing at first but an intelligently taken history plus anoscopic, sigmoidoscopic and digital examinations will usually reveal the correct diagnosis. Such a routine is discussed.

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NUTRITION

Diabetes Mellitus

By

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Importance of diabetes as a cause of death: Thirty years ago, Joslin (1) wrote "if diabetes should continue to increase in the next 30 years at the same rate statistics show it has increased in the last 30 years, it would rival tuberculosis as a cause of death." The statistics then were undoubtedly faulty, and, in fact, this statement was made to show that a fallacy existed somewhere. Developments since then, however, have made this prediction correct. At that time tuberculosis was first, and diabetes was twenty-seventh, in the list of the most lethal diseases. Since then, diabetes has moved up to the ninth position in the list of the most lethal diseases, and one condition only (premature birth) separates it from tuberculosis, which is in seventh place (2.3).* We hear and read much about deaths from motor vehicle accidents. According to recent vital statistics (4) the death rate from diabetes exceeded that from collisions between automobiles and trains; collisions between automobiles and street-cars; other automobile accidents; motor cycle accidents and all other motor vehicle accidents combined.

The magnitude of the problem of diabetes is appreciated only when consideration is given to (a) the relationship between age and the onset of this disease and (b) how the ages of general populations have been affected by achievements in medicine in general since the beginning of this century.

Relationship between age and onset of diabetes: Though diabetes occurs at all ages, even in early infancy,* it is essentially a disease of people approaching and past middle life. In 1940, the writer had the occasion to compare the age-sex distributions of diabetic populations with those of populations in general. The age-sex distributions of the diabetics were based upon 20,000 cases from the combined experiences of Dr. E. P. Joslin's Clinic in Boston (6) and his own at The Montreal General Hospital. The comparison with one of the general populations in

* See also The Canada Year Book, 1947 (Dom. Bur. Stat., Ottawa, 1947).

* The literature (5) records 57 cases under one year of age, and not all such cases are reported.

the past. Many more, therefore, marry and have children, and diabetes is to a very large extent an hereditary condition. In the group of cases to be reported here, the incidence of a family history of diabetes was 39.1 per cent, which corresponds almost exactly to that reported by Wilkerson and Krall (20).

The combined effect of all of the above factors is that the population of diabetics is increasing at a relatively greater rate than the general population. It has been estimated that from 1940 to 1950, the diabetic population will have increased by about 18 per cent; whereas, the total population will have increased by about nine per cent only (19).

Number of diabetics in Canada: It has been estimated there are now between 500,000 and 1,000,000 diabetics in the United States (19, 21). In 1946, by use of somewhat the same type of data, the writer estimated that there were about 45,000 diabetics in Canada, 18,091 males and 26,684 females. That this was a conservative estimate is suggested from an earlier study which gave the figure of about 100,000 (22). The percentage distributions of this diabetic population, according to age and sex, was approximately the same as in the United States. This is shown in Fig. 2.

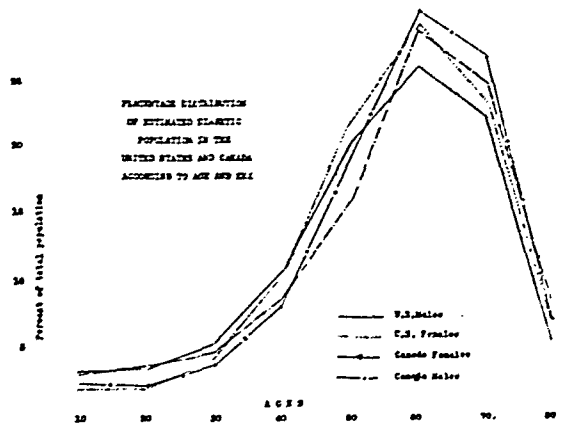


Fig. 2. —

Insulin supply and demand: One example of the diabetic problem is the supply and demand of insulin. Theoretically, the supply is unlimited. Actually, it is not unlimited, because the pancreas of cattle and hogs — beef, veal and pork pancreas — constitute the only sources of insulin which have as yet been found suitable for large scale production. Sheep pancreas is a very poor source. Assuming that 40 units per day is the average requirement per person, to satisfy the needs for 20 years, the average diabetic requires, approximately, 600 cattle or almost 4,000 hogs, and cattle and hogs are produced to supply meat and not to supply insulin. To produce them for insulin alone would be prohibitive economically. Fortunately, in Canada, there is no immediate prospect of a shortage — more is being produced than is currently being used;* but this is not the situation elsewhere, though the improvements in collecting and storing pancreatic glands for extraction of the insulin elsewhere is expected to aid the situation appreciably. It has been suggested that insulin should be produced from the islet tissue of fish, whales, etc., but, until means are available for doing this on a large scale economical basis, it may be that the only means of meeting the increasing demands in the future, because of the increasing population of diabetics, will be to find means of reducing the percentage of cases that require insulin or of decreasing the average dose per diabetic, and, as will be shown here, both are possible to a very appreciable extent.

Mortality statistics and progress: The increasing importance of diabetes as a cause of death in no way reflects the progress which has been made in the treatment of this disease during the last 35 years. Experiences with coma, tuberculosis and gangrene are examples.

Coma: In 1914, the situation for the severe diabetic was tragic; if he did not follow treatment, he died from coma; if he followed treatment, he died from starvation. Coma, which, in 1914, accounted for two-thirds of all of the deaths, is now, with extremely few exceptions, inexcusable. In the group of cases being reported here, there have been five cases only during the last five years and no deaths from it.

Tuberculosis: Tuberculosis, which was present in almost half of all the fatal cases, is now no more common in this group than amongst the general population of non-diabetics.

Gangrene: Amputations of legs for diabetic gangrene, common in the past, with a high mortality, had to be performed in three cases only in the group of cases being reported here during the last five years; and there were no deaths. Statistics are often difficult to interpret, because of the many variables, but one of the simplest procedures in statistics is to count amputated legs and dead people. The data also clearly show that the rule that premature arteriosclerosis is inevitable in cases of diabetes of five years duration no more holds, provided treatment is followed carefully (23, 24).

Juvenile diabetes: Most encouraging is also the the health of the diabetic who developed the condition in childhood; who followed treatment carefully, and who is now a fully mature adult; though most disastrous are the cases where treatment has not been followed carefully — blindness from diabetic retinitis, death from advanced nephritis and even coronary thrombosis at age 20 years (24).

The satisfactory experiences with coma, tuberculosis, gangrene and arteriosclerosis reflect the improvement of health in general. Living and existing are not synonymous, and the diabetic, provided he follows treatment, now lives; he no more merely exists. This to a very large extent is due to the improvements of the diabetic diets. No more are there indications for the unappetizing low carbohydrate-high fat diets. Present-day treatment permits an intake of 200 to

* Personal communication — Dr. A. M. Fisher, Secretary, Insulin Committee, University of Toronto.

250 and more grams of carbohydrate per day, which by proper substitution, permits sugar in tea and coffee; marmalade or jam on toast and, without exception, all fresh fruits and vegetables. Assuming a slice of bread to weigh, approximately, one ounce and a portion of butter five to six grams, by omitting two thirds of one slice of bread and one portion of butter, the diabetic may have an ice-cream cone. A glass of gingerale is equal to one slice of bread.

Ratios of Actual to Expected deaths: The combined results of all the advances may be seen in Fig. 3, reproduced from a previous report (25) and

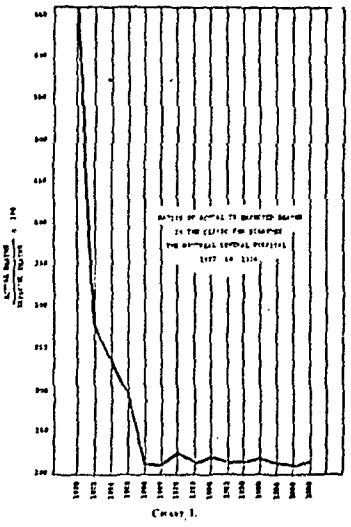


Fig. 3. —

in which are graphically recorded the ratios of actual to expected deaths in the Clinic for Diabetes at The Montreal General Hospital from the time of the discovery of insulin to the end of 1936. That these satisfactory conditions have been maintained in the group of cases with which this communication is concerned will be seen below.

Insurability of diabetics: Impressive, however, as the advances in the treatment of diabetes have been to physicians, by the sufferers from this disease, they have been regarded with much suspicion, and for very sound reason. If their chances of life were as good as claimed, why was it that life assurance companies persisted in their refusal to accept diabetics as policyholders? But this also has been remedied, to some extent at least.

In 1940, there occurred an event in the life of the diabetic in Canada about which there was no publicity, but which, in a manner more telling than words, pointed to the real progress which had been made in the treatment of this disease. A Canadian life insurance company — The Manufacturers Life Insurance Company — had entered a field which had hereto been shunned; they had decided to accept diabetics as policyholders.

It was, of course, necessary to exercise caution. As no company had insured diabetics wittingly before, there were no past experiences from which to translate the expectation of life of the diabetic into dollars and cents. It was, therefore, not only necessary to charge an extra premium, but this extra premium had to be arrived at empirically. Since, in a large number of people, the diabetes is discovered at 45 years, this was taken as the focal point. At this age, an additional premium of ten dollars per $1,000.00 covered a mortality of about 200 per cent of the normal. In order to cover the mortality over age 45 years, the premium of ten dollars was increased by one dollar per year increase of age. For example, at age 50 years, the premium was $15.00.

No policies were issued to people below age 30 or above age 60. It was also decided not to underwrite any individual who showed any impairment other than diabetes, with exceptions of slight changes of build.

The most important factor in considering any diabetic for insurance WAS NOT THE SEVERITY OF THE DIABETES, BUT THE CARE WITH WHICH TREATMENT WAS BEING FOLLOWED, which included the frequency with which the blood sugar was checked. An examination every four to six months was accepted as satisfactory.

With these precautions, early in 1945, the writer predicted that, in addition to improving the morale of diabetics by accepting them as policyholders, such practice would result in appreciable benefit to the Company, and both seem to have been realized.

In September 1946, the Company* had insured 280 diabetics, which represented a risk of $2,750,900.00, and, in the majority of cases, the diabetes was not mild; of these 280 people, 204 were being treated with insulin; the average dose of the group — not including the non-insulin cases — was 39.1 units. One diabetic was receiving 88 units per day.

In September 1947, the Medical Officer of the Company published the experience with 373 diabetics (26), representing a risk of $3,741,300.00, and, in the majority of cases, the diabetes was not mild. The largest daily dose of insulin was 115 units; the average, not including the non-insulin cases, was 38.3 units. Yet, in this group, there was one death claim only — much less than was expected.

Since then,* the number of policyholders has been increased to over 400 with a risk of over $4,000,000.00 and, in all, there have been four death claims only, one of which followed an operation for Diverticulitis of the Sigmoid Colon, a condition entirely unrelated to diabetes.

Four death claims only was much better than was expected; but they alone are not a reliable criterion. They give confidence in the method of selection employed, but they may have been due to luck. An

* Personal communication — Dr. R. C. Montgomery, Medical Officer, The Manufacturers Life Insurance Company, Toronto, Ont.

important question, for example, was this: Is there or is there not an inherent tendency for the diabetes to become worse? If there is, a factor to consider is the possibility of a piling effect — an ultimate death rate for which the above-mentioned extra premium does not allow. In experimentally produced diabetes in animals, no such tendency has been noted; but, as yet, no one has succeeded in producing diabetes in animals corresponding in every respect to human diabetes. In man, definite proof one way or the other was lacking, because no study had as yet been made of the relation between treatment and carbohydrate tolerance over such long periods as 10, 15 or more years.

Investigation: In March, 1946, therefore, with the cooperation of The Manufacturers Life Insurance Company, the writer commenced an investigation of all of his cases seen during the last 25 years, and the purpose of this communication is to record the findings to date.

1. SELECTION OF SUBJECTS

Since private patients are more likely to follow treatment carefully than those who do not pay for their examination, data of private patients afford a much more reliable index of the efficacy of any given form of treatment of diabetes than those of charity patients. Also, as a group, private patients conform more with life assurance policyholders than charity patients. This investigation was, therefore, restricted entirely to private cases.

2. RELIABILITY OF SAMPLE

The first step was determination of the extent to which the sample was representative of diabetic populations in general, at least with respect to age and sex. In Fig. 4 are, therefore, graphically recorded

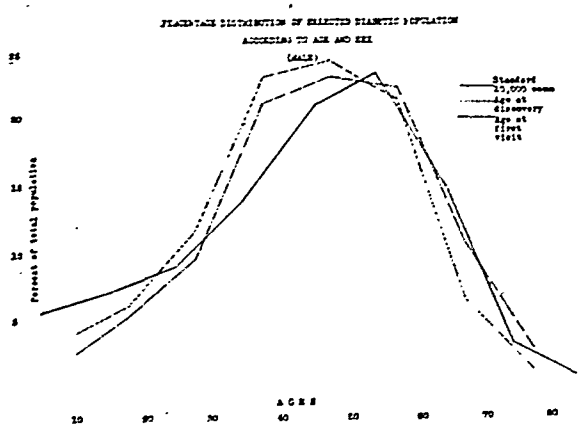


Fig. 4. —

the percentage distributions of the males according to age at the time of the discovery of the diabetes and also when first seen by the writer. In Fig. 5 are recorded the same findings in the female group. By comparing these curves with those of Fig. 1, it will be noted that the sample was reasonably representative of diabetic populations in general, at least with respect to age and sex — two important considerations in evaluating life assurance risks.

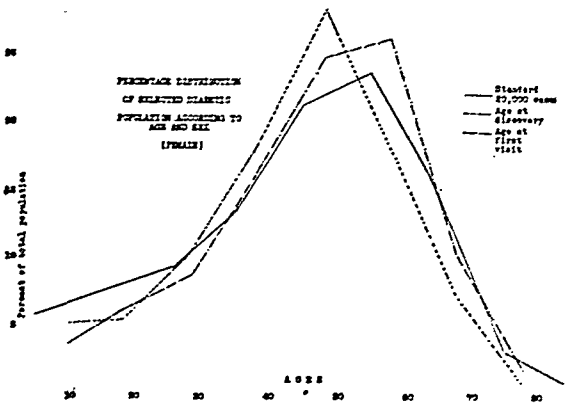


Fig. 5. —

3. THE PROBABILITY OF SUBSEQUENT DEVELOPMENT OF FRANK DIABETES IN DOUBTFUL CASES

i. A not infrequent experience at times, because of the complete absence of clinical signs and symptoms, is the need of determining whether a person is in fact a diabetic. The sugar was discovered in the urine accidentally in the course of an examination for life assurance, etc. The sugar was found in the urine on one occasion only — repeated tests thereafter failed to show it again. The blood sugar in the fasting state was repeatedly normal, and the blood sugar time curve was of a doubtful character, the only abnormality having been either a peak higher than the generally accepted upper limit of normality (0.180 per cent) or a lag in the development of the peak; the blood sugar was normal in the fasting state and, also, one, two and two and one-half or three hours after the administration of the glucose. In some cases, the blood sugar time curve, probably because of previous restriction of carbohydrates, may be perfectly normal.

Provided there are a sufficient number of such cases available and they have been observed for a period of ten or more years, one means of determining the significance of such findings is to determine the incidence of subsequent development of frank diabetes and the relationship between the latter and the treatment prescribed.

ii. Selection of subjects: For this investigation, therefore, no individual was included who had not been observed by the writer for at least ten years. In an appreciable percentage of cases, the periods of observation were fifteen years and more. In this group, there were 133 cases.

iii. Grouping of subjects: The cases were divided into two groups, namely, (a) those who had not been given treatment because of the possibility only of diabetes, but who had been advised to report periodically for examination as a precaution and (b) those who had been given treatment and who followed it. In the first group were also included those who had been given treatment but who, as the records showed, followed it for a short period of time only or very

irregularly. In view, also, of a family history of diabetes increasing the chances of diabetes, each group was further divided into (a) those with a family history of diabetes and (b) those with no such history.

iv. Comparison of data: In each case, the degree of disturbance of carbohydrate metabolism at the last examination, ten years or more later, was compared with that noted at the first visit. As stated, the only information sought here was the incidence of subsequent development of FRANK diabetes and its relation to treatment. The combined data are briefly summarized in Table I.

TABLE I.

Relationship between treatment and subsequent development of diabetes in cases with incomplete blood sugar time curves with and without a family history of diabetes.

Group	Family history	No. of Cases	Diabetes No.	Diabetes %
Total		133	39	29.3
	Positive	43	17	39.9
	Negative	90	22	24.4
Diet		84	18	21.4
	Positive	24	6	25.0
	Negative	60	12	20.0
No Diet		49	21	42.8
	Positive	19	11	57.8
	Negative	30	10	33.3

v. Results: It will be noted that, of the group as a whole, *29.3 per cent had developed frank diabetes* subsequently, and that the incidence of the latter was twice as high amongst those who did not receive treatment as amongst those who did.

It will also be noted that, regardless of any treatment, the incidence of subsequent development of frank diabetes was definitely greater amongst those with a family history of diabetes than amongst those with no such history. The highest incidence was in the group who not only had a family history of diabetes, but who had also received no treatment. It will be noted that 57.8 per cent of this group of doubtful cases had developed frank diabetes.

The combined data thus clearly indicate (a) the importance of sugar in the urine, even if found once only (b) the need of determining, in doubtful cases, whether there is or there is not a family history of diabetes and (c) the need of observing such individuals for a long period before assuming that they are not diabetics. None of these findings is new; but the extent to which they are important has not, to the writer's knowledge, been determined hitherto quantitatively.

4. SIGNIFICANCE OF BLOOD SUGAR TIME CURVES WHEN NORMAL OR WHEN THE ONLY ABNORMALITY IS A HIGH PEAK OR A LAG IN THE DEVELOPMENT OF THE PEAK

i. Selection and group of subjects: As stated, one of the reasons the above-mentioned subjects were investigated was the finding of an incompletely abnormal blood sugar time curve. For many years, because of a number of experiences (27), the writer has regarded such curves as indicative of diabetes, provided all conditions known to be capable of producing similar disturbances of carbohydrate tolerance have been excluded — infection, hyperthyroidism, etc. With this practice, however, as the literature clearly shows, there is by no means general agreement. Therefore, to test whether it is still warranted, the above-mentioned subjects were further grouped according to the character of the blood sugar time curve, namely, (a) normal curve (b) an abnormally high peak only (above 0.180 per cent) (c) peak of normal height, but a lag in its development, the peak having been noted at the end of an hour or more, instead of 30 minutes after the ingestion of the glucose and (d) both a high peak and a lag in its development. Each of the above-mentioned groups was then further divided into (a) those with a family history of diabetes and (b) those with no such history. The incidence of subsequent development of frank diabetes was then observed in each group. The combined data are briefly summarized in Table II.

TABLE II.

Relationship between type of incomplete blood sugar time curve and subsequent development of diabetes in cases with and without a family history of diabetes.

Group	Family history	No.	Diabetes No.	Diabetes %
Whole	Total	133	39	29.4
	+	43	17	39.9
	0	90	22	24.4
Peak only	Total	37	11	29.7
	+	14	6	42.8
	0	23	5	21.7
Lag only	Total	29	9	31.1
	+	11	5	45.4
	0	18	4	22.2
Peak + lag	Total	30	9	30.0
	+	8	3	37.5
	0	22	6	27.2
Normal curve	Total	37	10	27.0
	+	10	3	30.0
	0	27	7	25.9

ii. Results: It will be noted that, regardless of the type of curve — whether normal or otherwise — the incidence of subsequent development of frank diabetes was high — 21.7 to 45.4 per cent, and, again, the incidence of subsequent development of frank diabetes was greater amongst those with a family history of diabetes than in those with no such history. The data are thus definitely opposed to the practice of disregarding the blood sugar time curve because the only abnormality is a high peak or a lag in its development. By such practice, as the data clearly show, the chances are that early diabetes will be overlooked in an appreciable percentage of cases.

It will be noted that, amongst this group of cases, there were thirty-seven with perfectly normal blood sugar time curves — 27.8 per cent of the total — due probably to the common practice of reducing the carbohydrate intake in the interval between the dis-

covery of the glycosuria and the performance of the blood test. Nevertheless, 27.0 per cent of these individuals had developed frank diabetes subsequently. The importance of this finding, from the standpoint of evaluating life assurance risks, is obvious. Even though sugar is found in the urine on one occasion only, the chances, according to these experiences, are 27 in 100 that the person is potentially a diabetic and thus will manifest frank diabetes some years later, unless treatment is prescribed and followed. The chances of subsequent development of diabetes are still greater if there is also a family history of diabetes.

5. INDICATIONS FOR BLOOD SUGAR TIME CURVE

As in the writer's previous studies (27, 28) the relationship between the blood sugar in the fasting state and the type of blood sugar time curve was again investigated and the findings were essentially the same. With a blood sugar of 0.140 or more in the fasting state, it may be assumed that the blood sugar time curve will be definitely abnormal. There is, therefore, no need to subject the individual to the inconvenience and expense of such tests. In Table III are reproduced the comparative findings of a previous study of 1,346 cases.

TABLE III.

Relationship between fasting blood sugar and type (positive or negative) of blood sugar time curve*

Fasting Blood Sugars (Per cent)	Number of Cases	Diminished COH Tolerance Number of Cases	Percentage Incidence
0.121-0.125	421	277	64.6
0.126-0.130	236	191	80.9
0.131-0.135	198	173	87.3
0.136-0.140	125	121	96.8
0.141- +	366	365	100.0

* Rabinowitch, I. M.: Proc. Assoc. Life Ins. Med. Dir. of America, vol. 20, p. 11, 1933.

6. IS THERE AN INHERENT TENDENCY FOR THE DIABETES TO BECOME WORSE?

i. Statistically, the more severe the diabetes, the greater is the risk from coma and, thus, the shorter is the expectation of life. Therefore, a problem which had never been settled, and which it would appear the following data clarify, is whether there is or there is not, in the human diabetic, an INHERENT tendency for the diabetes to become worse. The importance of such information from the standpoint of evaluating life assurance risks requires no comment. In his experiments on partially depancreatized animals many years ago, Frederick M. Allen showed that there was no inherent tendency. From the following data, it would appear that this applies also to human diabetes.

ii. Selection of subjects: For this study, 100 individuals were selected at random, except for the following:

(a) In all cases, the diabetes was very mild at the first visit.

(b) In all cases, a blood sugar time curve was obtained at the first visit.

(c) No case was included unless the individual had been under the writer's observation for at least ten years.

iii. Grouping of subjects: The cases were then divided into (a) those with incompletely abnormal blood sugar time curves and (b) those with completely abnormal curves at the first visit. The curves obtained at the first visit were then compared with those noted (a) ten to fourteen years later and (b) fifteen or more years later. The combined data are briefly summarized in Table IV.

TABLE IV

INFLUENCE OF DIET UPON BLOOD SUGAR TIME CURVES FOLLOWING INJECTION OF GLUCOSE IN EARLY DIABETES

Type of First blood sugar time curves	Duration of Diabetes from Discovery of Glycosuria (Years)											
	All Cases				10 - 14				15 +			
	No.	B. S. T. C.*			No.	B. S. T. C.			No.	B. S. T. C.		
		Complete		Incomplete**		Complete		Incomplete		Complete		Incomplete
		No.	%	No. %		No.	%	No. %		No.	%	No. %
All types	100	36	36.0	64 64.0	76	41	54.0	35 46.0	24	15	62.5	9 37.5
Incomplete**	63	29	46.0	34 54.0	49	21	42.9	28 57.1	14	8	57.2	6 42.8
Complete	37	27	72.9	10 27.1	27	20	74.1	7 25.9	10	7	70.0	3 30.0

*B.S.T.C. = Blood sugar time curve
**No less than 3 abnormalities.
***Includes disappearance of any abnormality.

iv. Results: It will be noted, in the group as a whole, that sixty-three of the curves were incompletely abnormal, and thirty-seven were completely abnormal at the first visit. Of the sixty-three incompletely abnormal, thirty-four remained incompletely abnormal — an incidence of 54.0 per cent — after ten years or more. Of the thirty-seven completely abnormal, ten became incompletely abnormal — an incidence of 27.1 per cent.

There were seventy-six curves in the group of ten to fourteen years of observation. Of these, forty-nine were incompletely abnormal and twenty-seven were completely abnormal at the first visit. Of the forty-nine incompletely abnormal, twenty-eight remained incompletely abnormal — an incidence of 57.1 per cent. Of the twenty-seven completely abnormal, seven became incompletely abnormal — an incidence of 25.9 per cent.

Of the twenty-four curves in the group of fifteen years or more duration, fourteen were incompletely abnormal and ten were completely abnormal at the first visit. Of the fourteen incompletely abnormal, six remained incompletely abnormal — an incidence of 42.8 per cent, and of the ten completely abnormal, three remained completely abnormal — an incidence of 30 per cent.

The above data, alone, therefore, suggest that there is no inherent tendency for the diabetes in human individuals to become worse. In view, however, of downward progress in a very appreciable percentage of these cases, the next step was an attempt to correlate

progress with the care with which the treatment prescribed was followed.

v. Relationship between body weight and progress: Since the diabetes in these cases was very mild, frequent examinations were not indicated. All, however, were advised to reduce their weights, because of the risks from obesity in general. The most reliable overall evidence, therefore, of the care with which treatment was followed was the reduction of body weight in the overweight subjects to the "best" weights for the heights, according to life assurance company standards.

Table V shows that, amongst the above-mentioned

TABLE V

INFLUENCE OF DIET UPON BLOOD SUGAR TIME CURVES FOLLOWING INGESTION OF GLUCOSE IN CASES OF EARLY DIABETES WITH AND WITHOUT OBESITY*

Type of first blood sugar time curves	OBESITY					NO OBESITY				
	No.	Blood sugar time curves				No.	Blood sugar time curves			
		Complete		Incomplete			Complete		Incomplete	
		No.	%	No.	%		No.	%	No.	%
All types**	51	23	45.2	28	54.8	49	33	67.3	16	32.7
Incomplete	29	10	34.4	19	65.6	34	19	55.8	15	44.2
Complete	22	13	59.0	9	41.0	15	14	93.3	1	6.7

*In excess of 15 per cent of "Best" weights, according to Life Assurance Company Standards.
**Includes all cases of 10 years duration and over. (Group 15 years and over too small to be significant).

one hundred individuals, there were fifty-one with body weights in excess of 15 per cent of the "best" weights for their heights, according to life assurance company standards, and, amongst them, there were twenty-nine incompletely abnormal, and twenty-two completely abnormal, curves at the first visit. Of the twenty-nine incompletely abnormal, nineteen remained incompletely abnormal — an incidence of 65.6 per cent. Of the twenty-two completely abnormal, nine became incompletely abnormal — an incidence of 41.0 per cent.

Amongst the forty-nine individuals with no obesity, there were thirty-four incompletely abnormal, and fifteen completely abnormal, curves. Of the thirty-four incompletely abnormal curves, 15 — an incidence of 44.2 per cent — remained incompletely abnormal. Of the 15 completely abnormal curves, one only — an incidence of 6.7 per cent — became incompletely abnormal.

The only additional information here was that the presence of obesity AT THE ONSET OF THE DIABETES is a favorable sign. The information required was the influence of reduction of weight in the overweight subjects on carbohydrate tolerance ten or more years later. Glassberg (29) has shown that the more closely the weight approached the ideal the greater was the tendency for the appearance of a normal "tolerance" curve. The next step, therefore, was to divide the fifty-one cases of obesity into (a) those who had lost their obesity and (b) those who had not.

vi. Influence of reduction of weight on progress in cases of obesity: Table VI shows that, amongst

TABLE VI

INFLUENCE OF REDUCTION OF WEIGHT UPON BLOOD SUGAR TIME CURVES FOLLOWING INGESTION OF GLUCOSE IN CASES OF EARLY DIABETES WITH OBESITY*

Type of first blood sugar time curves	OBESITY					NO OBESITY				
	No.	Blood sugar time curves				No.	Blood sugar time curves			
		Complete		Incomplete			Complete		Incomplete	
		No.	%	No.	%		No.	%	No.	%
All types**	14	10	71.4	4	28.6	37	13	35.1	24	64.9
Incomplete	8	5	62.5	3	37.5	21	5	23.8	16	76.2
Complete	6	5	83.3	1	16.7	16	8	50.0	8	50.0

*In excess of 15 per cent of "Best" weights according to Life Assurance Company Standards.
**Includes all cases of 10 years duration and over. (Group 15 years and over too small to be significant)

the fifty-one cases of obesity, at the end of the period of observation, thirty-seven had lost their excess weights.

Amongst the fourteen whose weights were still in excess of 15 per cent of the "best" weights for the heights, eight had incompletely abnormal, and six had completely abnormal, curves, at their first visit. Of the eight with incompletely abnormal curves three only remained incompletely abnormal — an incidence of 37.5 per cent. Of the six completely abnormal curves, one only became incomplete — an incidence of 16.7 per cent.

On the other hand, amongst the thirty-seven individuals who had lost their obesity, twenty-one had incompletely abnormal, and sixteen had completely abnormal, curves at the first visit, and, of the twenty-one with incompletely abnormal curves, 16 — an incidence of 66.5 per cent — remained incompletely abnormal; amongst the 16 completely abnormal curves, eight — an incidence of 50 per cent — became incomplete.

vii. Conclusions: (a) Though the presence of obesity at the onset of the diabetes is a favorable sign, such individuals are likely to show a loss of carbohydrate tolerance unless they lose their excess weight.

(b) The combined data support the view that there is no inherent tendency for the diabetes to become worse; that, in fact, provided treatment is followed, there is a tendency towards improvement of carbohydrate tolerance. As stated, the importance of this finding, from the standpoint of evaluating life assurance risks, requires no comment.

7. INVESTIGATION OF MORE ADVANCED CASES

The above conclusions, having been based upon experiences with very mild cases of diabetes only, are of limited significance. The next step, therefore, was consideration of the experiences with more advanced cases.

i. Selection of subjects: For this purpose, 1,500

individuals were selected at random, except that no period of observation dated back further than 1931. This year was selected because the writer's high carbohydrate-low calorie diet was not instituted until 1930 (30) and because of the changed outlook of the diabetic noted with this diet. Though the low carbohydrate-high fat diets had undoubtedly controlled the diabetes from the standpoint of the blood and urine sugar, the nutrition in general, was not very satisfactory; weakness and undue fatigue, for example, were common; neuritis was common, and a striking feature in women in the child-bearing period was frequent disturbance of menstruation and, quite often, complete amenorrhoea for periods of many months and even for years. Much of this was due to the difficulty of maintaining nitrogen equilibrium with low carbohydrate-high fat diets; whereas, one of the striking effects of the above-mentioned high carbohydrate diet is nitrogen retention (31). The lowest urinary excretions of nitrogen ever noted in man have been noted with this diet only (32). This diet, also, judging from all published data, has resulted in the most striking reductions and in the lowest average value, of the cholesterol content of the blood plasma in diabetes (23, 33).

ii. Grouping of cases: Though the diabetes in these cases was more advanced than the above-mentioned group, obviously not all were of the same severity. For practical purposes, therefore, these 1,500 diabetics were further divided into three groups, as follows:

(a) MILD: No clinical signs or symptoms suggestive of active diabetes. Glycosuria discovered accidently and either transient or post-prandial only. A blood sugar of 0.140 per cent or more in the fasting state or 0.180 per cent or more at any other time of the day; but both glycosuria and hyperglycemia readily controlled by QUALITATIVE restriction only of diet.*

(b) MODERATELY SEVERE: Clinical signs and symptoms generally present — weakness, undue fatigue, etc.; glycosuria persistent, but no acetone bodies, and readily controlled by QUANTITATIVE diet — definite quantities of carbohydrates, fat and protein — without the aid of insulin.

(c) SEVERE: Satisfactory clinical and laboratory control** not possible without the aid of both quantitative diet and insulin.

Blood sugar time curves were not obtained in any of these cases, in view of the fact that in none was the diabetes very mild. Also, a number of variables would have had to be considered in the moderately severe cases, in order to interpret changes of carbohydrate tolerance and not all are controllable. In order, therefore, to determine whether there is or is not an inherent tendency for the diabetes to become worse, it was considered advisable to restrict the studies to severe cases only, that is, those who not only required QUANTITATIVE diets, but also insulin.

iii. Insulin requirements of diabetics on quantitative diets: Table VII shows that, amongst this group

TABLE VII

INSULIN REQUIREMENTS OF DIABETICS ON QUANTITATIVE DIETS

				Whole Group	Own Cases	Others
TOTAL NUMBER				1500	476	1024
INSULIN:	Number			580	116	464
	Per cent			38.6	24.8	45.3
	Discontinued:	Number		116	32	84
		Per cent		20.0	27.6	18.2
	Reduced:	Number		166	51	115
		Per cent		28.6	43.9	24.8
	Units:	Insulin cases only:	First dose	39.1	30.9	41.2
			At last visit	24.9	22.3	26.4
		Whole group:	First dose	15.1	7.6	18.6
			At last visit	7.7	3.9	15.4

of 1,500 diabetics, 580 only required insulin — an incidence of 38.6 per cent. Amongst the latter, 166 — an incidence of 28.6 per cent — have been able to reduce the insulin dosage, and 116 — an incidence of 20 per cent — have been able to discontinue its use entirely. The average number of units at the beginning of insulin treatment was 39.1, and, at the last visit, it was 24.9 units. This includes the insulin cases only. For the whole group (insulin and non-insulin cases combined) the average dosage was 15.1 units at the beginning of the insulin treatment and 7.7 at the last visit.

iv. Influence of previous treatment upon insulin requirements: For many years, it has been the writer's experience that, regardless of the degree of severity of the diabetes, more difficulties have been encountered in individuals who, when seen by him for the first time, had received treatment previously than in those for whom treatment was prescribed for the first time. Analysis of the data clearly showed that, in a large number of the cases, this was due to previous use of "free" diets — permitting the patient to eat any food desired and in the amounts desired — and attempt to balance the food so eaten with insulin. This practice has always been condemned by the writer as well as by Dr. E. P. Joslin and others; but, judging from recent experiences, the practice is increasing. That the practice is bad may be seen in the following data obtained by dividing the above-mentioned insulin-treated cases into (a) the writer's and (b) others, that is, those who, when first seen by the writer, had not, as yet, received any treatment and those who, when first seen by him, had been under different forms of treatment for different periods of time. The combined data are briefly summarized in the same Table (Table VII).

It will be noted that, of the 1,500 cases, 476 were "the writer's" and 1,024 were "others." Amongst the 476 of "the writer's" cases, 116 only — an incidence

* No sugar in tea or coffee; no pastries; puddings, etc.; lean meats, limited quantities of bread, potatoes, butter and cream.

** Urine free from sugar and acetone bodies; blood sugar normal or nearly so in the fasting state — no higher than 0.140 per cent. No clinical signs.

of 24.8 per cent— required insulin; whereas, of the 1,024 "others," 464 required insulin — an incidence of 45.3 per cent. Of the 166 of the "writer's" cases, 32 were able to discontinue the insulin — an incidence of 27.6 per cent; whereas, amongst the 464 "others," 84 — an incidence of 18.2 per cent —only were able to do so. The average number of units amongst "the writer's" at the beginning of insulin treatment and at the last visit were 30.9 and 22.3 respectively; whereas, amongst the "others," the values were 41.2 and 36.4 units respectively.

The extent to which the difficulties with the "free diet" cases was due to liver damage is not known. In such cases, as is well known, hyperglycemia and glycosuria are very common. In children, the liver is very frequently enlarged and, in both children and adults, the urinary excretions of urobilinogen are frequently very large (34). It is of interest here to note that somewhat similar experiences have been met with in the treatment of diabetic coma. In a previous report (35) it was shown that our own cases seemed to have a better chance of recovery from the coma than those not seen before the onset of the coma. The data are briefly summarized in Table VIII.

TABLE VIII

Influence of previous diet upon chances of recovery from diabetic coma.

Period		Own cases	Others
Before 1931*	Number of cases	39	24
	Deaths: Number	10	8
	Per cent	25.6	33.3
Since 1931**	Number of cases	79	40
	Deaths: Number	14	20
	Per cent	17.7	50.0
Since 1931** (Adjusted for severity)	Number of cases***	30	8
	Severity Index	18.2	20.0
	Deaths: Number	2	5
	Per cent	6.6	62.5
Since 1937**** (Adjusted for severity)	Number of cases***	28	9
	Severity Index	18.4	20.0
	Deaths: Number	2	6
	Per cent	7.1	66.6

*Low carbohydrate-high fat diets
**High carbohydrate-low calorie diets
***Cases include only those with Severity Index calculated from all nine factors.
****Change in method of treating diabetic coma.

It will be noted that, even in the early days, when the diets were very low in carbohydrates and high in fat, whereas, the mortality amongst the previously treated cases was 25.6 per cent, it was 33.3 per cent amongst the patients who had been seen for the first time. Since 1931, that is, since use of the high carbohydrate-low calorie diet, the data were still more suggestive.

Limited significance was to be attached to these findings, since no consideration had been given to the severity of the coma. The next step, therefore, was to adjust for severity by use of our Severity Index (25). After having done so, however, it will be noted that, whereas, amongst the cases treated previously with the high carbohydrate-low calorie diet, the mortality was 6.6 per cent only, in the cases seen for the first time, with approximately the same Severity Index, it was 62.5 per cent. In 1937, the method of treatment diabetic coma was changed (36), but that this difference of mortality was due to the previous treatment and not to the change of the treatment of coma, is clearly seen in the same Table, where the comparison is restricted to the cases of coma since 1937. It will again be noted that, whereas, amongst the patients who had been treated previously with the high carbohydrate-low calorie diet, the mortality was 7.1 per cent only, the mortality amongst the patients seen for the first time was 66.6 per cent.

v. Relationship between degree of control of diabetes and ability to reduce or discontinue insulin treatment: Amongst the points which The Manufacturers Life Insurance Company stresses in selection of applicants, is not the severity of the diabetes, but the CARE WITH WHICH TREATMENT IS BEING FOLLOWED. This method of selection, as will be seen, is fully supported by the findings in this study.

As a statistical index of the degree of the control of the diabetes, the Control Index, which the writer reported some time ago, was employed (23). It is by no means as satisfactory as he should like to see it; but, being at least to some extent QUANTITATIVE, it is better than no quantitative index at all. In calculating the Index, a value of 3.0 is assigned when the blood sugar is perfectly normal; the value is 2.0 when the blood sugar is increased, but still below 0.180 per cent; a value of 1.0 is given when the blood sugar is above 0.18 per cent, and the value is zero if, in addition to sugar, the urine also contains acetone bodies. Two examples of the necessary calculations are shown in Table IX and

TABLE IX

Calculation of Control Index

	Rating (a)	No. (b)	(a x b)	C. I.
Example 1:	3	18	54	
	2	13	26	
	1	4	4	84 ÷ 35 equals 2.40
	0	0	0	
		35	84	
Example 2:	3	2	6	
	2	13	26	
	1	14	14	46 ÷ 33 equals 1.39
	0	4	0	
		33	46	

the combined data are briefly summarized in Table X.

It will be noted that, in the 1,500 cases as a whole, the average Control Index was 2.24. In the non-insulin cases, it was 2.41 and, in the insulin cases, it was 1.95.

Amongst the insulin cases, the average Control Index amongst those who were able to discontinue the insulin was 2.25; amongst those who were able to reduce the dosage, it was 2.09, and, amongst the remainder, the average was 1.77 only.

TABLE X

Relationship between degree of control of diabetes and ability to reduce or discontinue insulin treatment

Group		All Cases		Own		Others	
		No.	C. I.*	No.	C. I.*	No.	C. I.*
Whole		1500	2.24	476	2.38	1024	2.18
No Insulin		920	2.41	360	2.45	560	2.39
Insulin	All cases	580	1.95	116	2.06	464	1.93
	Discontinued	116	2.25	32	2.21	84	2.26
	Reduced	166	2.09	51	2.11	115	2.08
	Other**	298	1.77	33	1.83	265	1.76

* *Control Index (See* Rabinowitch, I. M., Ann. Int. Med., 8, 1436, 1935).

** Insulin dosage stationary or increased

Here, also, it will be noted the data clearly show that, when the cases were divided into "the author's" and "others," on the whole, the average control of the diabetes was better amongst "the author's" than amongst the "others." It is thus clear that the ability to reduce insulin dosage or discontinue its use entirely is not influenced by some inherent tendency, but is to a very large extent dependent upon the degree of the control of the diabetes. Spiegelman and Mosenthal (37) have shown that carbohydrate tolerance may be increased by diet.

vi. General conclusions: Combining all of the findings, therefore, of (a) the very mild and doubtful cases (b) the mild cases — those who required qualitative restriction only of food intake (c) the moderately severe — those who required quantitative diets, but no insulin and (d) the severe — those who required insulin, the evidence seems clear that THERE IS NO INHERENT TENDENCY FOR THE DIABETES TO BECOME WORSE, regardless of the severity of the disease: that, in fact, provided treatment is followed, there is a very appreciable expectation of improvement of carbohydrate tolerance. The average diabetic, therefore, who is accepted as a policyholder by the above-mentioned method of selection employed by The Manufacturers Life Insurance Company is a good risk, provided he continues to follow treatment, which, it would appear, explains to a large extent the Company's satisfactory mortality experiences to date.

8. METHODS OF ESTIMATING BLOOD SUGAR AND THEIR EVALUATION

1. Picric acid v other methods: Since Bang (38) first introduced a satisfactory and clinically applicable method for quantitative estimation of blood sugar, numerous methods have been devised. They include both macro and micro procedures; but though the values obtained by some approximate true blood sugar values more than others — some very closely — without exception, all include reducing substances other than glucose — uric acid, creatinine, glutathione, ergothione, cysteine and undetermined substances (39, 40, 41, 42). For example, amongst the early changes from the picric acid procedures — Lewis-Benedict (43) Benedict (44) Myers and Bailey (45), etc. — the Folin-Wu (46) and Folin ferricyanide methods (47, 48) yielded values about 20 mgms. per 100 cc. less than the picric acid methods. The experiences with more recent methods, such as Somogyi's (49, 50) are approximately the same; but none of the values represents glucose only. In a study, in 1928, the writer (51) found that the non-fermentable reducing substances fluctuate within a narrow range — 16 to 31 mgms. per 100 cc. Folin and Svedberg (52) reported lower values, and, by use of a micro-method (53) Mosenthal (42) reported higher values.

2. Interpretation of blood sugar tests: The fact of practical importance here, in the early detection of diabetes, is that, though the newer blood sugar methods yield lower values, the standards of normality commonly employed, as may be seen in the literature, are those which had been arrived at by the picric acid methods. For example, when it is stated that, normally, the blood sugar in the fasting state ranges between 0.08 and 0.12 per cent, and that the maximum level of the peak of the normal blood sugar time curve is 0.18 per cent, the values quoted are those which had been established by the picric acid method. Joslin (21), for example, accepts a blood sugar of 0.120 per cent as the upper limit of normality in the fasting state and so do Matthews, McGrath and Berkson (54). It is obvious, therefore, in view of the above-mentioned experiences with the cases about the diagnosis of which there was doubt at the first visit, if such values are accepted as standard with use of the more recent methods, very early diabetes will be overlooked in an appreciable percentage of cases.* For these reasons, though other methods have been employed by the writer for research purposes, every blood sugar test during the last 25 years for diagnosis and for estimating the degree of control of the diabetes in cases under treatment has, without exception, been obtained by the Meyers-Benedict picric acid method slightly modified by the writer and with use of highly purified picric acid (55). One advantage of this method is that the glucose standard in picric acid solution, if kept in a dark bottle, keeps almost permanently, regardless of the room temperature. It is with this method only that diabetes is assumed by the writer to exist, if, in the absence of clinical signs or symptoms of conditions known to be capable of producing hyperglycemia, the blood sugar is 0.140 per cent or more in the fasting state or above 0.18 per cent any time after ingestion of any form of food.

3. Capillary blood sugar tests: Another possible source of error is use of capillary blood — Bang, Hagedorn, Jensen, McLean, etc. The chief error possible here is diagnosis of diabetes when it does not exist. As is well known, capillary blood is a mixture of arterial and venous blood, and, though the sugar contents of both in the fasting state are approximately the same, after ingestion of glucose, the arteriovenous difference is variable and unpredictable (56) because the sugar content in the arteries may be very appreciably higher than that in the veins (57). It is for this reason, in addition to other possible pitfalls in use of micro-clinical methods referred to by the writer previously (27) that micro-chem-

* Even a peak of 0.170 per cent after a meal or after ingestion of glucose is too high, in view of the known differences between the picric acid values and those obtained by the newer methods.

ical methods have never been employed by him either in routine or research. Joslin (21) warns about the higher values with capillary blood than with venous blood. Langner and Fies (56) have done so also. Even the standard adopted by Joslin with capillary blood, namely 0.200 per cent, if found after a meal (21), though a wise precaution from the standpoint of prevention, may, at times, deprive a non-diabetic of the benefits of life assurance.

9. RELATIVE SENSITIVITY OF THE BLOOD SUGAR IN THE FASTING STATE AND AFTER MEALS FOR THE EARLY DIAGNOSIS OF DIABETES MELLITUS AND ESTIMATION OF DEGREE OF CONTROL OF CASES UNDER TREATMENT

i. Procedures in common use: Various procedures are employed in use of blood sugar tests for diagnosis and as an index of the degree of control of the diabetes in cases under treatment — examination in the fasting state, one-half hour after a meal and one, two and three hours, etc. In view, therefore, of the uniformity of the blood sugar data in the writer's cases with respect to the method of estimation, consideration was given to the relative sensitivity of the blood sugar in the fasting state and after meals for the above-mentioned purposes.

ii. Tests for early diagnosis: As for the blood sugar time curves, amongst the single determinations, there were tests performed in the strictly fasting state and one-half hour, one hour, two hours and three hours after food. Meyers and McKean (58) and, also, Leyton (59) have not found the blood sugar after a meal dependable. On the other hand, according to Wishnofsky and Kane (60) food tolerance tests do not differ significantly from "glucose tolerance" tests. With this, the writer agrees, provided the sample of blood is obtained at the proper time. In Table XI are briefly

TABLE XI

Relative sensitivity of blood sugar tests in fasting state and after meals for early diagnosis of diabetes mellitus (500 cases — Random selection)

Time	No.	Blood Sugar (%) Max.	Min.	Avge.
Fasting state	166	0.166	0.064	0.098
1/2 hr. after meal	46	0.238	0.158	0.201
1 hr. after meal	53	0.256	0.153	0.169
2 hrs. after meal	122	0.209	0.089	0.121
3 hrs. after meal	113	0.169	0.082	0.102

summarized the experiences with 500 blood tests selected at random in cases in many of which the diagnosis was doubtful at first, but which were found to be diabetic from a number of experiences.

It will be noted that, though there were wide differences between the maximum and minimum values, and though the minimum at some periods after food was within the normal limits, that is, below 0.180 per cent; the most sensitive test after an ordinary meal for early detection of diabetes was at the one-half hour period. As Mosenthal has pointed out (61), the blood sugar in the fasting state may be misleading — early diabetes may be overlooked — if the blood sugar is normal. According to Sindoni (62) one to three hours, generally two hours, is the interval of choice. It will be noted, however, that, at the two and three-hour periods also, the average blood sugar was within the normal limits in these very early cases. The most sensitive test, as stated, is the blood sugar at the ONE-HALF HOUR period, thus, fitting in with the above-mentioned experiences with blood sugar time curves obtained after administration of glucose. It will be noted that the values in the average column correspond exactly to the typical blood sugar time curve following ingestion of glucose in a very mild diabetic, the only abnormality being a peak above the generally accepted maximum level of 0.180 per cent.

iii. Relative sensitivity of blood tests in the fasting state and after meals for diagnosis in the same individuals: As stated, the above-mentioned average values were obtained by random sampling. Much more reliable, therefore, would be a similar study, but comparison of the blood sugar obtained in the fasting state with that noted at different times after meals in the SAME INDIVIDUALS. This study was, therefore, made and the data are briefly summarized in Table XII.

TABLE XII

Relative sensitivity of blood tests in fasting state and after meals in the same individuals for early diagnosis of diabetes mellitus

Time	No.	Blood Sugar (%) Max.	Min.	Avge.
Fasting state	18	0.166	0.068	0.097
1/2 hr. after meal		0.256	0.169	0.155
Fasting state	29	0.147	0.074	0.111
1 hr. after meal		0.244	0.164	0.177
Fasting state	86	0.143	0.076	0.095
2 hrs. after meal		0.232	0.074	0.111
Fasting state	67	0.161	0.087	0.102
3 hrs. after meal		0.250	0.093	0.107

It will be noted that the findings were essentially the same: in the fasting state, and two hours and three hours after food, the average blood sugar was perfectly normal; whereas, at the one-half hour period, it was 0.188 per cent — just slightly above the generally accepted maximum level of normality, namely, 0.180 per cent and, therefore, the most sensitive test.

A point of practical importance to be noted is that the most marked hyperglycemic response to ingestion of carbohydrates is after the MORNING MEAL; in general, the lowest peak is after the noon meal, and the rise is intermediate after the evening meal. For the very early detection of diabetes, therefore, if the blood sugar is to be examined after a meal, the most sensitive test is after breakfast.

iv. Tests as an index of the degree of control of the diabetes in cases under treatment: As stated, one of the criteria in the evaluation of life assurance risks is the care with which treatment is followed and this is judged to a large extent by the blood sugar. There-

fore, here, also it was necessary to determine the most satisfactory time for the test. For this purpose, therefore, 3,000 tests were selected at random, and it will be noted (Table XIII) that though wide differences were noted between the maximum and minimum values as in the above-mentioned tests for early diagnosis, the highest average blood sugar was noted at the one-half-hour period.

TABLE XIII

Relative sensitivity of blood sugar tests in fasting state and after meals as an index of degree of control of diabetes (3000 tests — Random selection)

Time	No.	Blood Sugar (%) Max.	Min.	Avge.
Fasting	1773	0.333	0.036	0.143
1/2 hr. after meal	104	0.434	0.166	0.204
1 hr. after meal	126	0.526	0.151	0.185
2 hrs. after meal	386	0.357	0.082	0.164
3 hrs. after meal	611	0.302	0.074	0.153

It will be noted that much higher values are recorded here than in Tables XI and XII. This was due to the fact that the data, having been obtained by random sampling, included the most severe as well as the mildest cases. They were also from records of those who did not follow treatment carefully as well as those who did. However, though all values in the average column are definitely higher than the normal, the average in the fasting state and three hours after a meal, were, approximately, the same, and definitely lower than at the one-half hour period; in the fasting state, it was 0.143 per cent and, three hours after a meal, it was 0.153 per cent. It was slightly higher two hours after a meal, namely, 0.164 per cent; whereas, at the one-half hour period, it was 0.204 per cent and, therefore, was the most sensitive test.

v. Relative sensitivity of tests as an index of the degree of control of the diabetes in the same individuals in cases under treatment: Since these data were also obtained by random sampling, here, also much more reliable would be a similar study, but comparison of the blood sugar obtained in the fasting state with that noted at different times after meals in the SAME INDIVIDUALS. This study was, therefore, made and the data are briefly summarized in Table XIV.

TABLE XIV

Relative sensitivity of blood sugar tests in fasting state and after meals in the same individuals as an index of control of diabetes

Group	No.	Blood Sugar (%) Max.	Min.	Avge.
Fasting		0.277	0.036	0.135
1/2 hr. after meal	82	0.434	0.166	0.196
Fasting		0.270	0.119	0.151
1 hr. after meal	72	0.385	0.151	0.178
Fasting		0.333	0.053	0.147
2 hrs. after meal	160	0.357	0.099	0.169
Fasting		0.416	0.043	0.139
3 hrs. after meal	186	0.295	0.074	0.158

It will be noted that the findings were essentially the same.

Influence of form of treatment: The fact that the findings were essentially the same in Tables XIII and XIV suggested a fallacy somewhere, in view of the common experience that, except in very early diabetes, the peak of the blood sugar time curve occurs at the one-hour period or later and not at the end of 30 minutes. Consideration had to be given to the possible need of grouping the cases according to the treatment, in view of (a) the fact that these data included many insulin-treated cases and (b) the different behavior of insulin depending upon the type. For example, with protamine zinc insulin, though the blood sugar may be perfectly normal in the fasting state, the latter may be very deceptive (63); in spite of a normal blood sugar in the fasting state, there may be thirst and polyuria and, in addition to marked hyperglycemia and glycosuria, even acetonuria, due to the slow action of this form of insulin. With unmodified insulin, if the meal is taken too soon after the injection, the blood sugar may reach its peak at the one-half hour period, but, at the three-hour period, will probably be perfectly normal, because of the full and more powerful action of this rapidly acting insulin. In the case of unmodified insulin, therefore, the best indication of control would appear to be the blood sugar at the three-hour period. With globin insulin, the blood sugar will probably be lower during the day than with protamine zinc insulin, because of its more rapid action, but higher than with protamine zinc insulin in the fasting state, because it does not possess the same degree of prolongation of action.

In view of the above observations, 500 cases were selected at random and grouped according to the form of treatment, namely, (a) no insulin (b) unmodified insulin — two injections a day (c) protamine zinc insulin — one injection per day and (d) globin insulin — one injection per day and (d) globin insulin — one injection per day. The average values of the blood sugars obtained in the fasting state, and one-half hour and one, two and three hours after meals were then calculated. The combined results of 4,666 tests are briefly summarized in Table XV.

RELATIONSHIP BETWEEN FORM OF TREATMENT AND MAXIMUM, MINIMUM AND AVERAGE BLOOD SUGARS* IN THE FASTING STATE AND AFTER FOOD.
(4666 tests)

PERIOD	NO INSULIN				UNMODIFIED				PROTAMINE ZINC				GLOBIN			
	No	Blood sugar* Max	Min	M	No	Blood sugar* Max	Min	M	No	Blood sugar* Max	Min	M	No	Blood sugar* Max	Min	M
Fasting	1728	256	63	126	412	333	63	161	162	222	31	119	103	434	78	173
1/2 hr.	166	285	153	196	92	312	74	231	48	454	45	201	22	357	91	241
1 hr.	184	295	169	221	82	344	112	216	35	476	161	232	31	385	129	211
2 hrs.	534	244	123	187	166	238	51	171	89	434	139	221	51	302	74	168
3 hrs.	382	218	99	159	189	227	43	122	101	312	117	163	79	250	55	141

*Mgms. per 100 c.c.

The following are to be noted:

Non-insulin cases: The average blood sugar in the fasting state was only slightly above the normal. The highest average blood sugar was found at the ONE-HOUR period, fitting in with the more common experience. The lowest average blood sugar after

food was found at the three-hour period, namely, 0.148 per cent.

The fact that the average blood sugar was higher at the one-hour period in the non-insulin group; whereas, in Tables XIII and XIV, the peak was noted at the one-half hour period, seemed to confirm the need of grouping the cases in accordance with the form of treatment. That such grouping is essential is seen in the insulin-treated cases. Thus:

Unmodified insulin: The average blood sugar in the fasting state was above normal. The highest blood sugar was noted one-half hour after food. At three hours, the average was lower than in the fasting state and practically normal.

Protamine zinc insulin: The average blood sugar in the fasting state was within the normal limits. The highest average blood sugar was found one hour after food. The lowest average blood sugar after food was at the three-hour period, but, also differing from unmodified insulin, definitely higher than in the fasting state.

Globin insulin: The average blood sugar in the fasting state was higher than in all of the other three groups. The highest average blood sugar, as with unmodified insulin, was noted one-half hour after food. The lowest average blood sugar after food was at the three-hour period; it was definitely higher than with unmodified insulin; but definitely lower than with protamine zinc insulin.

Attention is drawn to the high maximum values in the non-insulin group of cases to emphasize the fact that a high blood sugar is, by itself, not an indication of the severity of the diabetes. Such findings are common in obese diabetics, without any clinical signs or symptoms of active diabetes. Where there are no clinical signs or symptoms, the glycosuria having been discovered accidentally, qualitative restriction of food intake alone generally suffices to render the urine free from sugar and the blood sugar normal very rapidly and, such individuals, provided they follow treatment carefully and, thus, lose their obesity, do well without the aid of insulin. By prescribing insulin merely because of such high blood sugars, severe diabetes is not differentiated from mild. Therefore, by including such cases in studies on insulin requirements, wrong conclusions about insulin and carbohydrate tolerance are almost inevitable.

Combining all of the findings, therefore, in the interpretation of the degree of control of the diabetes, in evaluating life assurance risks, the data clearly show the need of relating the blood sugar to the time the test was done and both to the form of treatment the applicant is receiving.

In view of (a) the random selection of the data and, thus, the inclusion of careless as well as careful patients and (b) the large number of observations — 4,666 tests — the average values found would appear to be reliable standards for evaluating risks, provided they were associated with satisfactory mortality experiences. The next step, therefore, was to calculate the ratio of actual to expected deaths in the group as a whole. However, since the data included those of individuals who did not follow treatment carefully as well as those who do, the obese diabetics were separated from those of normal weight or underweight. The cases were also grouped in accordance with the average degree of control of the diabetes, as estimated by the Control Index.

10. RATIO OF ACTUAL TO EXPECTED DEATHS

i. Method of calculation: Determination of mortality by calculation of the ratio of actual to expected deaths has been a routine in the writer's cases during the last 25 years (25). The extent to which these data may be employed in evaluating life assurance risks is not known, because of the method of their calculation. As they were meant entirely for comparative studies, the selection of Life Tables differed from that employed by life assurance companies. For example, for the purpose of this investigation, though the data included all of the cases of the last fifteen years, one Life Table only was employed, that is, U. S. Life Tables and Actuarial Tables 1939-1941 (13). The ratios of actual to expected deaths for this study were calculated as follows:

Commencing with 1932, the age-sex distribution of this group of diabetics was first determined. Then, by use of the values for 1000 qx for the different ages in the above-mentioned Life Tables, the expected number of deaths was calculated for that year in the whole group. In order to calculate the expected number of deaths in the following year (1933), one year was added to every one alive at the end of 1932; then, by applying the above-mentioned values 1000 qx of the different ages to the new ages, the expected number of deaths was determined for 1933. This procedure was continued to the end of 1947.

ii. Relationship between reduction of body weight and mortality in cases of obesity: With the above mentioned limitations in mind, an attempt was made to determine the influence of obesity upon mortality. For this purpose, amongst the 1,500 cases, there were 521 diabetics who, at their first visit, were overweight for their heights, according to the "best" weights of life assurance company standards. These individuals were divided into two groups, namely, (a) those who were overweight at their last visit and (b) those whose weights were not in excess of 15 per cent of the "best" weights for their heights. The ratio of actual to expected deaths was then calculated for each group. The data are summarized briefly in Table XVI.

TABLE XVI

Relationship between reduction of body weight and mortality in cases of obesity*

Group	No.	a/e**
Total***	521	139.7
Obesity	288	156.8
No obesity	233	118.6

* In excess of 15 per cent of "Best" weight, according to Life Assurance Company Standards.

** Ratio of Actual to Expected Deaths (U. S. Life Tables and Actuarial Tables — 1931-1941).

It will be noted that, when the cases were divided into (a) those whose weights were normal and (b) those whose weights were in excess of 15 per cent of the "best" weights for their heights, according to life assurance company standards, the ratio of actual to expected deaths was 156.8 per cent in excess of the normal amongst those who did not follow the treatment prescribed and thus failed to lose weight; whereas, it was 118.6 per cent only amongst those who followed treatment and, at their last visits, were found to have lost the necessary weight.

iii. Relationship between degree of control of diabetes and mortality: To determine the relationship between the degree of control of the diabetes and mortality, 1,000 cases were selected at random and grouped according to the degree of control of the diabetes. Since the degree of control of the diabetes varied widely in some cases, the cases were divided into three groups according to the AVERAGE Control Index. The ratio of actual to expected deaths was then calculated for each group. The data are briefly summarized in Table XVII.

TABLE XVII

Relationship between control index and mortality

Control Index Range	Average	No.	a/e*
Total	2.13	1000	124.3
-1.50	1.21	79	226.2
1.51-2.00	1.78	182	156.2
2.01-3.00	2.32	739	105.8

* Ratio of Actual to Expected Deaths (U. S. Life Tables and Actuarial Tables - 1939 - 1941)

It will be noted that quite a striking relationship was found. With a Control Index of 2.01 to 3.00, the ratio of actual to expected deaths was 105.8 per cent of the normal only; whereas, with a Control Index of 1.50 and under, which indicates persistent glycosuria and also occasional acetonuria, the ratio was 226.2 per cent of the normal.

A fact to be noted here is that though limited significance is to be attached to these findings, because of the above-mentioned use of Life Tables, the latter are of recent date and, therefore, contain the lowest 1000 qx values. The ratios, therefore, are definitely higher than they would have been had the older Life Tables been employed for the corresponding years.

Combining all of the findings, therefore, as they include diabetics who have been careless, as well as those who have been careful, in following the treatment prescribed, and as it is not possible to determine the extent to which treatment will be followed carefully in the future, the average blood sugar values shown in Table XV in relation to the form of treatment, when combined with the ratios of actual to expected deaths noted, would appear to be reliable standards of control for evaluating life assurance risks.

SUMMARY

Attention is drawn to the increasing population of diabetics and to its causes and, thus, to the importance of diabetes as a public health problem.

The satisfactory mortality experiences with insured diabetics are briefly discussed; but, in view of the possibility of these having been due to chance, it was necessary to determine whether in man, as in experimentally produced diabetes, there is no inherent tendency for the diabetes ultimately to become worse.

Since private patients are more likely to follow treatment carefully than charity patients, and since they also conform more to life assurance policyholders otherwise, this investigation was restricted entirely to private patients.

A study of the percentage distribution of the group according to age and sex showed that the sample was representative of diabetic populations in general, at least with respect to these two variables.

Amongst this group, there were cases in which the diagnosis of diabetes was doubtful, because of the absence of clinical signs; transient glycosuria; repeatedly normal blood sugars in the fasting state and incompletely abnormal blood sugar time curves.

By dividing the cases into those for whom treatment was prescribed and those who were given no treatment, but advised to be examined periodically, as a precautionary measure, a high incidence of subsequent development of frank diabetes was noted amongst those who had received no treatment, and the incidence was higher amongst those with a family history of diabetes than amongst those in whom no such history was obtainable. The data thus clearly emphasized the importance of glycosuria, even if found on one occasion only, and, also, the importance of the family history in such cases.

The incidence of subsequent development of frank diabetes in cases in which the only abnormality of the blood sugar time curve was a high peak or a lag in the development of the peak was determined in the above-mentioned group and was found to be high, and higher amongst those with a family history of diabetes than amongst those in whom no such history was obtainable. The data are thus opposed to the common practice of ignoring such curves in the diagnosis of diabetes. By such practice, an appreciable percentage of cases of very early diabetes may be overlooked.

In the study of the indications for blood sugar time curves, the findings of the previous studies were confirmed. Blood sugar time curves are not necessary, if the blood sugar in the fasting state is 0.140 per cent or higher.

Comparison of blood sugar time curves obtained at the first visit with those ten or more years later in cases with and without obesity indicated that obesity, at the onset of the diabetes, is a favorable sign: but, loss of carbohydrate tolerance occurs in an appreciable

percentage of such cases if the excess body weight is not reduced.

Comparison of blood sugar time curves obtained in very mild cases at the first visit with those obtained ten, fifteen or more years later showed no evidence of an inherent tendency for the diabetes to become worse.

Comparison of the insulin requirements at the first and last visits, showed no evidence of an inherent tendency for the diabetes to become worse in severe diabetes.

Evidence is presented showing that the increasing practice of use of "free diets" is definitely harmful. A definite relationship was noted between the degree of control of the diabetes and carbohydrate tolerance, judging from the ability to reduce or discontinue insulin treatment.

Methods of estimating blood sugar are briefly discussed, and attention is drawn to possible harmful effects of use of more recent methods for estimating blood sugar; but in the interpretation of the findings, use of standards based upon the older methods which yield higher blood sugar values.

The relative sensitivity of blood sugar tests obtained in the fasting state and at different times after food for diagnosis and determination of the degree of control of the diabetes were investigated. For early detection of diabetes, the most sensitive test was found to be the blood sugar one-half hour after a meal, which agrees with the experience with blood sugar time curves. As an index of the degree of control of the diabetes in cases under treatment, the best time for the blood sugar test depends upon the form of treatment.

According to the method employed for calculating ratios of actual to expected deaths, a definite relationship was noted between obesity and mortality and also between the degree of control of the diabetes and mortality. Though limited significance is to be attached to the data, because of the method employed for calculating the ratios, the relationship noted between obesity and mortality was definite. The relationship noted between the degree of control of the diabetes and mortality was still more striking.

The combined data clearly indicate that, of the criteria now being employed for selecting diabetics as life assurance policyholders, the care with which treatment is being followed is the most valuable.

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Nutrition Notes

Is Dietary Treatment Useful in Hypertension?

Frederick M. Allen 28 years ago suggested the value of a salt-free diet in essential hypertension. (The term "essential" as applied to hypertension differentiates it from that accompanying nephritis, hyperthyroidism and other states known to cause hypertension). For at least 30 years, some practitioners have prescribed lowered protein diets in essential hypertension, although it was difficult to see any benefits from such treatment. Indeed the low protein diet not infrequently produced weakness and even anemia without any perceptible improvement in the blood pressure levels other than might be expected from asthenia and its influence on smooth muscle throughout the body. Recently Allen has re-affirmed his confidence in the good effects of salt-free diet when continued over a period of many years and admits that the chlorine radical in salt is not important, thus inferring that the sodium radical is the important one to be omitted. It appears to be the general consensus of opinion that the "rice diet," where it benefits hypertension, does so by reason of its low sodium content, although it should be remembered that this diet is also poor in protein.

That the whole story of hypertension still is full of mystery is suggested by the recent work, particularly that of Selye, and his associates at the University of Montreal, which tends to view certain disease states as the results of endocrine overstimulation under stress. Hypertension is one of these diseases which is believed to result from an initial severe stress affecting the anterior lobe of the pituitary gland, then the adrenalin gland and finally the kidney. According to this concept, a variety of non-specific damaging agents evokes in the organism a "general adaptation syndrome" whose nature is dictated, not by the specific nature of the insult, but rather by its severity and duration. The initial shock or "alarm reaction" is accompanied by a pronounced catabolic tendency with wide-spread cellular damage in many organs and a breakdown of body proteins. This results in a flooding of the blood stream with protein degradation products and proteolytic enzymes. The anterior lobe is influenced to produce excessive amounts of corticotrophin which, in turn, cause swelling of the adrenal cortex and increased production of adrenal corticoids. One of the proved effects of this hypersecretion of adrenal corticoids is to induce a

renal type of hypertension and nephrosclerosis.

Following the initial stress comes a "period of resistance" (which represents the prolonged hypertension seen clinically in such instances). Finally, in the "period of exhaustion" we are dealing with cardiac failure, uremia and/or cerebral disease. It is suggestive that a diet rich in protein greatly facilitates the production of corticotrophin — indeed the anterior lobe is unable to pour forth a flood of corticotrophin except in the presence of a fairly high protein diet.

This new work on the "alarm reaction" is fascinating. That it will ever explain essential hypertension is open to question. But it appears that in *malignant hypertension* a trial of a rice and fruit diet may be advisable. It would provide the low sodium and low protein intake presumably beneficial to nephrosclerosis of hormonal origin. In this connection it should be recalled that in China, where the rice diet is habitual and universal, hypertension of any kind is rare. A few years ago among one thousand patients in a Chinese hospital, only one was found to have an elevated blood-pressure and she was a nurse who had just completed her training in the United States.

Apparently, high amounts of sodium and protein in the diet are two metabolic conditions favorable to the production of hypercorticoidism, the latter being the essential factor in producing the general adaptation syndromes, of which certain types of hypertension are leading examples. This by no means suggests that all cases of hypertension will benefit from low protein-low sodium diet.

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Human Botulism in Australia

David F. Gray* describes two widely separated outbreaks of botulism in man, the first to be recorded in Australia occurring in November and December 1942. Canned beets appeared to be the foodstuff responsible. In both instances the cans were abnormal ("blown") and the beets had a peculiar color, odor and taste. *Cloistridium botulinum,* type A or type B, were responsible. Probably more cases would have developed had not other defective and infected cans been discarded. Probably the disease has not been reported in Australia before because commercial canning, prior to the second world war had been restricted to the safer acid fruits and vegetables, and home canning of non-acid foodstuffs has never been as popular in Australia as in America. Beet root is one of the few canned vegetables which is often eaten without pre-heating. The author points out that botulinus toxin is unstable to heat and also alcohol. In one outbreak in England the only survivor was one who had drunk whisky with his meal.

Clinically, the cases showed normal or subnormal temperatures. Diminished power of ocular convergence was common, and also bilateral ptosis of the eyelids. Death was due in all fatal cases to bulbar paralysis. Those who escaped death required about two months to recover. Antitoxin was not used in any of the 28 cases.

Obviously *any* commercial can which is "blown" should be discarded. Canned beet root ought to be heated before being eaten. Probably a can infected with botulinus smells so badly and looks so abnormal, as a rule, that the average person would discard it.

* Gray, D. F.: Human botulism in Australia. Med. J. Australia, July 10, 1948, Vol. 35, No. 2, 37-42.

Nutrition in India

It is difficult, at this distance, to form any adequate conception of the nutritional conditions in India today, immediately following liberation. But, by reading between the lines of what literature is available, it seems certain that optimal conditions of nutrition obtain nowhere in India except perhaps in the homes of the few very wealthy citizens while, at the other extreme, there are shifting areas of starvation or serious under-nutrition widespread throughout the entire Indian peninsula. The chief and most critical problem is the lack of adequate calories for the masses, owing to the fact that rice production, for example, does not approach in volume the potential consumption, even on a bare maintenance level. There exist increasing profiteering and black-marketing, so difficult to control in such a period of flux as now obtains in India, and the facilities for food preservation are absent or very poor. There is practically no commercial refrigeration and the people themselves as a rule do not understand the simplest methods of canning. Primary among the problems of nutrition in India is the lack of a source of protein of good biological value. Grazing is on the increase but it may require twenty years before milk and meat products rise to any appreciable level of adequacy. The medical profession of India are presumably immune to the indigenous religious teachings which place a severe interdiction upon the eating of meat, but it is questionable if even medical leadership will ever be able to overcome so ancient a custom as that which renders a cow a sacred object. It is probable, however, that the physicians of India soon will increase popular knowledge of what we today regard as adequate nutrition, and will also stimulate methods of agriculture, grazing and food preservation to the lasting benefit of the Indian people.

Abstracts on Nutrition

GLASS, W. H.: *Non-vitaminic factors involved In the production of the "small intestinal deficiency pattern."* (Gastroenterology 10, 4, 660 April 1948).

Glass proves that an abnormal jejunal mucosal pattern can be caused by multiple factors other than vitamin B complex deficiency. Abnormalities in the outlet of the stomach, which produce irregularity in the size of the bolus, produce radiographic patterns in the jejunum which are abnormal. These findings do not preclude the validity of the diagnosis of vitamin B complex deficiency or idiopathic steatorrhea when mechanical factors, as presented by Glass, are excluded.

In the first reported case a duodenal spasm was apparently associated with emotional disturbance. The roentgenogram showed an advanced abnormal small intestinal pattern. The patient responded to antispasmodics and psychotherapy, not to B complex. In the second case an organic pyloric obstruction was present. The abnormal small intestinal pattern was rectified by surgical short circuiting. The third case was that of a duodenal ulcer with normal pattern. Following improvement of the ulcer symptoms, reexamination at the time of a Meniere's seizure showed delayed gastric emptying with advanced jejunal changes. Another case had a partial obstruction of the post-pyloric region and at the site of a gastro-enterostomy stoma with advanced jejunal changes. There was no response to vitamin B complex treatment, but subsequent subtotal gastrectomy with a well functioning stoma resulted in a normal jejunal pattern.

It is important to realize that there may be many factors involved in producing the so called "deficiency pattern" of the small intestines.

FRANZ J. LUST

BENNIKE, T.: *Folic acid treatment of pernicious anemia.* (Nordisk Med., Aug. 6, 1948, V. 39, No. 32, 1451-1456).

Twelve patients with Addisonian pernicious anemia were treated with folic acid (Lederle) or various Danish preparations of synthetic folic acid. Suboptimal hematological and clinical remission was seen in all cases. Subacute combined degeneration of the spinal cord, present in three cases, was unaltered by folic acid therapy, and in one patient slight neurological complications began during folic acid administration, after 35 days of treatment. Improvement in these conditions followed upon subsequent liver extract injections.

EMERSON, K., JR.: *Nutrition in diabetes.* (Nutrition Rev., Sept. 1948, V. 6, No. 9, 257-259).

At present there is a tendency to use a somewhat lower carbohydrate and total caloric intake than normal to avoid obesity and reduce insulin requirements, but most agree that the diet of a diabetic should vary little from that of a normal person. Actually, increasing the intake of carbohydrate increases the efficiency of insulin. Young diabetics are more sensitive to insulin than older patients, and should be maintained on a relatively high carbohydrate intake. Yet overfeeding should be avoided, since permanent diabetes has been produced in cats merely by prolonged administration of excessive glucose. Arteriosclerosis is related to excessive cholesterol and fats in the blood and probably is abetted by poor dietary and insulin regulation. Eggplant and the Jerusalem artichoke lower the level of cholesterol in the serum. Ergostanol has been found to help control the extra skeletal deposition of calcium in animals. Diabetic retinitis has been found to improve under the use of a high protein diet and so has hepatic fatty infiltration. The best means of prophylaxis against primary diabetic neuritis is adequate administration of vitamin B-Complex, and its prolonged use in treatment gives gratifying results.

FLACHS, A.: *Nicotinamide treatment of pellagrous diarrhea, "pellagra without pellagra."* (Nordisk Med., Aug. 13, 1948, V. 39, No. 33, 1507-1509).

Twenty-two cases of diarrhea observed at the Old People's Home at Copenhagen were treated with niacin amide. All the cases had previously been unsuccessfully treated by ordinary obstipants. Only two of the cases had cutaneous pellagrous manifestations. In 17 of the cases the nacin amide therapy proved successful. A dose of 15 to 30 mgm. daily usually produced improvement in one to five days. One of the cases that did not respond proved to be colonic cancer.

STRANSKY, E. AND DAUIS-LAWAS, D. F.: *Iron deficiency anemia in early infancy (congenital iron deficiency anemia),* (Acta Medica Philippina, April-June, 1948, V. IV, No. 4, 43-52).

Four definite cases and one questionable case of congenital iron deficiency anemia are reported. In all cases, the evidence that the mother is suffering from severe iron deficiency anemia was obtained. If there is an iron deficiency anemia in the first four to six months of life of an infant, and the mother is likewise suffering from an iron deficiency anemia, and the anemia of both mother and infant is microcytic and hypochromic and neither is hypoplastic or infectious, then congenital iron deficiency anemia must be considered. While exceptionally rare in the Western countries, it appears to be widespread in the Far East.

BERGQUIST, N.: *Migraine cases examined from the allergic point of view.* (Nordisk Med. Sept. 3, 1948, V. 39, No. 36, 1600-1603).

The author studied 27 genuine cases of migraine in women, using 27 normal controls of the same age and sex, with a view to determine whether or not allergy was a significant factor in producing the disease. The patients showed no increased frequency of known allergic manifestations (asthma, hay-fever, nettle-rash or eczema) nor did their families. Eosinophilia of more than four per cent was present in four of the 27 migraine patients, but two of these had other allergic manifestations which could explain the eosinophilia. Alimentary allergy was suspected from some of the patients' histories and from some positive skin tests to food extracts. Attempts were made to provoke migraine attacks on at least two occasions each, within 30 minutes to three hours of consuming the food.

GIBSON, J. P.: *Advances in infant nutrition.* (Texas State J. Med., Sept. 1948, V. 44, No. 5, 358-360).

Premature infants do better on partially-skimmed cow's milk than human milk because of the greater protein and mineral content. Human blood plasma resembles colostrum and may with advantage be given orally to premature infants. It is now possible, when necessary, to maintain adequate nutrition by intravenous injections of glucose, amino-acids and even specially prepared homogenized emulsions of olive oil or lecithin. Special formulas ought not to be prescribed for newborn infants, since they ought to be allowed to get hungry prior to nursing. All infants should be fed when hungry and clock-feeding given up. A new trend in prescribing formulas is the reduction and early elimination of the carbohydrates added to the formula, as this practice produces healthier, leaner babies. Strained meat may be added to the formula of infants as young as six weeks. The substitution of ascorbic acid for orange juice eliminates orange juice allergy. Solid foods are started by the second or third month. New foods should always be introduced one at a time at intervals of about five days to detect the cause of any allergy which may appear. After six months, much of the milk should be replaced by solid foods. Coarser foods may be begun at about eight months of age. In children one year or older, "self-selection" of foods has much in its favor. Appetite is much decreased after the first year because of the slowing down of the growth curve and too much anxious solicitation on the mother's part is inadvisable. Vitamin B is usually prescribed "for the mother's benefit." Nearly all children love hamburgers, and tomato, lettuce, mayonnaise, relish, shredded cabbage and carrots can be administered via the hamburger which, with a glass of milk, makes a "wonderful" meal.

SHELDON, W.: *Celiac disease.* (Brit. Med. J., Sept. 25, 1948, 594-597).

The author decries the use of the term "celiac syndrome" and maintains that *celiac disease* is a definite clinical entity of unknown etiology which usually can be distinguished from fibrocystic disease of the pancreas on clinical grounds alone. Trypsin, lipase and amylase are produced in normal amounts by celiac children and the steatorrhea is not readily to be explained. Celiac disease must be differentiated from fibrocystic disease of the pancreas and also tuberculosis of the mesenteric lymph glands which, by blocking fat absorption, often results in marked steatorrhea. The flat oral-glucose absorption curve in celiac children has as yet not been convincingly explained. Reduction of starch in diet is of importance, fat should be kept at normal feeding levels and protein intake increased.

SUNDARESON, A. E.: *Protective action of nucleic acid on the liver in carbon tetrachloride poisoning.* (J. Indian Med. Assn., June 1948, V. 17, No. 9, 287-290).

It was found that oral administration of nucleic acid to experimental rats 48 hours prior to the injection of large doses of carbon tetrachloride had the effect of reducing the extent of liver damage as compared with that seen in control animals. Infiltration of the center of the lobule and the portal canals with mononuclear cells was an outstanding feature in the livers of many of the experimental animals. The author feels justified in presuming that the addition of foodstuffs rich in nucleic acid would exert a protective action in case of liver damage caused by toxins in the human being.

Editorial

AN INTERNIST LOOKS AT CARCINOMA OF THE GALL BLADDER

ALL MEDICAL TEXT BOOKS and papers written on carcinoma of the gall bladder stress the relationship of cholelithiasis and urge early removal of the organ when stones are present. It is my purpose to review this subject a little further to see whether there are any other factors in addition to the cholelithiasis which may play a part in producing carcinoma of the gall bladder.

Pathologists state that about 5% of all carcinomas start in the gall bladder; and carcinoma of the gall bladder ranks sixth in frequency of malignancy of the gastrointestinal tract. At the New England Deacon-

ess Hospital in routine postmortem examinations, carcinoma of the gall bladder was found in 1/2 of 1%. Of 1336 cases in which cholecystectomies were done at the Lahey Clinic, primary carcinoma of the gall bladder was found in 1.2%, and of these 70% were women. From the records at the Montefiore Hospital (1934-1944) of 586 cholecystectomies and 48 cholecystotomies, carcinoma of the gall bladder was found in 11 cases of a percentage of 1.7. The most accurate estimate from autopsy records of a large general hospital showed the general incidence of gall-bladder carcinoma to be 1/4 to 3/4% of all autopsies or 5% of the total of all cancer disclosed at autopsies. Judd and Gray in a series of 22,365 operations on the biliary tract found 212 cases of carcinoma of the gall bladder or approximately 1%. From the above statistics one can readily see that there is but a slight variance in the incidence of carcinoma of the gall bladder.

The age distribution is the same as for carcinoma elsewhere in the body, and the danger of carcinoma of the gall bladder is especially great in women past 40. This can be easily understood when we realize that the ratio of gall stones in females to males is about 5 to 1. It is also important to note that cholelithiasis is a very frequent condition occurring in from 10 to 20% of all adults.

Nearly all writers give as the most probable cause, an irritative factor based on the relationship of calculi to carcinoma. Frerichs in 1861, in his treatise on diseases of the liver, remarked on the relationship of gallstones to carcinoma of the gall bladder. It has been definitely established that stones are nearly always found in these cases. The incidence of calculi in cancerous gall bladders has varied from 69% (Musser) to 100% (Janowski). In the group of 11 cases of carcinoma of the gall bladder at the Montefiore Hospital, all but one showed many stones, and in the remaining case the presence of calculi was questionable because its presence or absence was not mentioned. Why stones should be the primary factor in carcinoma of the gall bladder is not precisely clear. That chronic local irritation predisposes to cancer has been more or less the accepted hypothesis, especially of the surgical group. One must be reminded of the fact that cancer has been found in the gall bladder which has no stones and in those in which stones had been previously removed by cholecystostomy. Some investigators are of the opinion that there is a radio-active carcinogenic agent in the stones themselves or that there is a tissue irritant which acts in the presence of a high concentration of cholesterol (Leitsch). Harold Burrows has made a very extensive study of the prolonged irritation by calculi. He placed gall stones and other foreign bodies in the gall bladders of 50 guinea pigs who lived for periods ranging from nine to 59 weeks. In no instance had carcinoma of the gall bladder developed. He regarded these results as supporting evidence that chronic irritation per se is not the cause of cancer.

Now as to the carcinogenic substance being a factor, it is definitely known today that cholic acid and deoxycholic acid have a close structural similarity to methylcholanthrene, a highly potent carcinogen. In the investigation on carcinogens during the past few years, a number of problems have been clarified (Lewisohn). The time period elapsing between the application of the carcinogen and the first occurrence of tumors depends upon the potency and quantity of the carcinogen, on the solvent on which the carcinogen is applied, on the mode of administration to the experimental animal, and also upon the strain of the animals used. Heredity and sexual maturity of the animals have a strong influence upon the latent period and yield of the tumors. A number of other constituents of the animal and human body such as cholesterol, Vitamin "D," male and female sex hormones are also structurally related to methylcholanthrene. In a recent analysis of the trends in carcinoma research (Murphy), the possibility that carcinoma tendency may be secondary to or dependent upon some other inherited condition is stressed. In conclusion, Dr. Murphy states that the degree of potentiality for malignancy is a variable quantity for each *tissue* or *cell* type, and this degree is determined largely, if not entirely, by heredity or a predisposing factor.

In the preceding paragraphs we have described the incidence of calculi in carcinoma of the gall bladder and various possible other factors that may enter into this process. It is well to comment here on the frequency of silent stones as disclosed by Dr. H. E. Robertson in his lengthy review entitled "Silent Stones." A survey of the post-mortem studies of the gallbladders made at Mayo Clinic during the ten years from 1934 to 1943, disclosed the fact that 1027 (497 males and 530 females) over the age of 20 years had gallstones. The histories of each patient were reviewed, and it was found that in 61% of this group neither the patient nor his attending physician was suspicious of the presence of gallstones. We can derive from this that gallstones may be completely silent throughout the life of a patient. It is Robertson's further contention that "the necessity for physicians to recognize that silent gallstones do actually exist, and the obligation to assume toward them a conservative attitude appear eminently logical." Boas emphasizes that should these silent stones be accidentally discovered in symptomless patients, the stones should be ignored, but the patient should be informed of their presence in case obscure symptoms arise subsequently.

Since in my analysis there are the other factors in addition to the gallstones which may produce carcinoma of the gall bladder, I cannot agree with the opinion of the surgical writers who insist that *all* cases of cholelithiasis should have surgical removal of the gall bladder in order to prevent carcinoma of the gall bladder. All cases of cholelithiasis and cholecystitis must be managed individually, surgery being advisable only in such cases where definite symptoms of dyspepsia or colic are present and especially so in those cases where there is a family history of apparent predisposition to carcinoma of the gastrointestinal tract.

SUMMARY

1. Calculi alone despite their high incidence have not been proven the cause of carcinoma of the gall bladder.

2. The other factors in the etiology of carcinoma of the gall bladder are possibly heredity or the potentiality for malignancy which is present in each tissue or cell type.

3. All cases of cholelithiasis or cholecystitis should be managed individually.

4. Conservatism is advisable in all silent gallstone cases.

5. Surgery is indicated when symptoms exist and where there is an apparent family history of carcinoma of the gastrointestinal tract. — LAWRENCE WECHSLER, M.D. Pittsburg, Pa.

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Book Reviews

AN INTRODUCTION TO GASTROENTEROLOGY. Walter C. Alvarez, M.D. 4th Edition, Revised and Enlarged. Paul B. Hoeber, Inc. New York. 1948. Pp. 903. Price $12.50.

This book contains practically everything that can be of use to the physiologist or the gastro-enterologist on the motor functions of the digestive tract. If only because of its splendid bibliography, medical librarians have always kept a copy within reach. For instance, if a physician wants to find Bayliss and Starling's classic article on the bowel, or Cannon's first article on X-ray studies of the digestive tract, or Lester Dragstedt's first article on vagotomy, there is the reference.

In this edition, 125 pages have been added, pages in which over 400 articles and books have been abstracted and their material added. As a result, the bibliography now contains some 2800 titles.

A great advantage of this book is that in discussing each subject, Alvarez has brought together all available information not only from the field of the physiologists but also from those of comparative anatomists, comparative physiologists, roentgenologists, and clinicians. The book is full also of information obtained from the German, French and Italian literatures.

This is such a storehouse of facts that every medical library has to have a copy, and every physiologist and every gastro-enterologist who does any research or writing will find the book of great help to him. There is so much that is interesting in the book that it can be read for pleasure as well as profit. For a young man going seriously into this study of gastro-enterology, the last chapter on books and reading and where to go to find information is alone worth the price of the book.

The volume represents the results not only of Alvarez' own studies in the Clinic and laboratory, but the fruits of nearly forty years of reading. As Alvarez says, he wrote the book largely to help his younger brethren in gastro-enterology so that they might start off at the level of their elders' scientific shoulders. He wanted to save them the effort of years of reading.

Our most unqualified recommendation of this monumental work goes without saying.

DANGER! CURVES AHEAD! By Miriam Lincoln, M.D., F.A.C.P., Pp. 138, ($2.50). The MacMillan Company, New York, 1948.

The title of this book is clever and so also is the approach to the subject. It may be safely recommended to the obese patient, especially an obese woman. The author is clinical assistant professor of medicine, University of Washington and naturally knows her psychology as well as her calories. She recommends "talk" while eating and suggests that a copy of Webster's dictionary be kept handy, should an argument arise over a word. This is typical of the thoroughness displayed by the delightful author. MacMillan's medical editors deserve a pat on the back for several popular books on obesity, among which it is very difficult to make a choice.

OVERWEIGHT IS CURABLE. By Wilfred Dorfman, M.D. and Doris Johnson, Pp. 160 ($2.75). The MacMillan Company, New York, 1948.

This book is written for the obese individual to read, and might well be recommended by the physician. In the veritable snow-storm of popular books about food and related nutritional problems this is a flake of unusual perfection, inasmuch as the material presented is in no way distorted and aims at *encouraging* the person who unfortunately has become too fat. Specimen diets are provided.

THE SKIN DISEASES. by James Marshall, M.D. 362 pp. Cambridge, at the University Press: New York, The MacMillan Company, 1948, $7.50.

This is a profusely illustrated and practical treatise on dermatology which is strongly recommended to practitioners and students.

THE BRITISH ENCYCLOPEDIA OF MEDICAL PRACTICE: (MEDICAL PROGRESS 1948). Butterworth and Co., Ltd., London, England, 1948.

Under the editorship of Lord Horder, some 15 medical authorities present succinct accounts of that which is of topical interest at the present moment in various fields of medicine, surgery, obstetrics and gynecology, cardiology, aviation medicine and other special fields. The book is, therefore, virtually a "year book" covering the entire field of practice and while it is attractively written, it naturally suffers from the defects of brevity. More than half the volume is occupied with general abstracts.

General Abstracts Of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

GALAGAN, D. J.: *Effect of topically applied flouride on dental caries experience.* (Public Health Reports, Sept. 1948, V. 1948, V. 63, No. 38, 1215-1220).

The use of calcium chloride as a supplemental treatment to applications of a two per cent solution of sodium fluoride does not enhance the caries-inhibitive action of sodium fluoride alone. The applications of fluoride are most effective when spaced at weekly or two weekly intervals. A one per cent solution of sodium fluoride is as effective as a two per cent solution. Application by spray is as effective as by cotton applicator.

YJERTZ, A.: *The treatment of cardiospasm by forced dilatation.* (Nordisk Med., Aug. 13, 1948, V. 39, No. 33, 1495-1499).

In a series of 67 cases of "achalasia cardiae" forcible dilatation caused complications in three cases. The end results were regarded as good in the vast majority of cases, after an observation period of seven years. The author thinks his cases have taught him the truth of Hurst's opinion, viz., that there is no true spasm associated with this disease. In cases in which true spasm was present it was later found that there was carcinoma of the cardiac region of the stomach.

MELLANBY, M. AND MELLANBY, H.: *The reduction in dental caries in five year old London school children (1929-47).* (Brit. Med. J., Aug. 28, 1948, 409-413).

An investigation of 1590 children in London indicated marked and progressive improvement in the incidence of caries as compared with previous surveys and this is thought to be due to the increased calcifying properties of the diet in England, especially the increased availability and use of milk, eggs and codliver oil.

STOMACH

MANNING, ISAAC HALL JR., AND HIGHSMITH, GEORGE P.: *Proplapse of the gastric mucosa through the pyloric canal into the duodenum.* (Gastroenterology, 10, 4, 643. April 1948).

Sixteen cases are reported in which the clinical and roentgenologic findings were considered consistent with a diagnosis of prolapse of the gastric mucosa through the pylorus into the duodenum. No distinctive syndrome was found, but symptoms referable to the upper gastro-intestinal tract were present in all but one case.

The characteristic roentgenologic finding consists of a circular, "mushroom" or "umbrella" filling defect in the base of the duodenal bulb, often associated with narrowing and elongation of the pyloric channel, and often with antral spasm and enlarged antral rugae.

Uncomplicated cases of prolapsed gastric mucosa, especially when associated with hypertrophic gastritis, may be treated with a medical regimen. Surgical treatment, such as excision of the redundant mucous membrane and pyloroplasty, is indicated only in cases of pyloric obstruction, ulceration with recurrent hemorrhages not prevented by medical therapy, severe anemia due to chronic blood loss, polyp formation with malignant degeneration, and suspected malignancy.

FRANZ J. LUST

HARDT, LEO L., SCHWARTZ, STEVEN O., AND STEIGMANN, FREDERICK.: *Gastroscopic observations in pernicious anemia.* (Gastroenterology, 10, 1, 108. January 1948).

One hundred patients with pernicious anemia were studied gastroscopically, 47 of them on two or more occasions. Atrophy of the stomach mucosa is not an invariable accompaniment of pernicious anemia, occurring in only 59% of the reported series. The atrophy of the gastric mucosa was not related to the length of time the disease was present, the amount of previous liver therapy, or the existing blood picture. Only a small per cent (nine out of forty seven) of the patients showed improvement in the appearance of the mucosa while under liver therapy, while four previously normal mucosas showed atrophy on re-examination.

Polyps were found in seven patients, and a proved carcinoma in one patient — the latter developing while the patient was under liver therapy.

Repeated X-ray and gastroscopic studies are indicated in every patient with pernicious anemia to discover as early as possible the presence of gastric carcinoma.

FRANZ J. LUST

BOWEL

MACHELLA, THOMAS E. AND MILLER, T. GRIER.: *Treatment of idiopathic ulcerative colitis by means of a "medical ileostomy" and an orally administered hydrolysate-dextri maltose mixture.* (Gastroenterology, 10, 1, 26-45. January 1948).

The method employed and the results obtained in the treatment of 14 cases of idiopathic ulcerative colitis are presented. The method aims to provide a temporary period of rest for the diseased intestine by means of a "medical ileostomy" and at the same time improve the nutritional status of the patient.

The ileostomy is accomplished by intubating the bowel to a point just proximal to the diseased area with a Miller-Abbott tube and by maintaining constant suction so as to prevent the small intestinal content from entering the diseased part. The alimentation consists in the oral administration of a solution of equal parts of an enzymatic casein digest and of dextri-maltose for varying periods of time after which gradually increasing amounts of substantial foods low in residue, are ingested. Essential vitamins and iron are supplemented.

Objective evidence of improvement consisted in a cessation of fever, a disappearance of anorexia and of the stigmata of vitamin deficiency, a return in the number and the character of the stools to normal, a gain in weight, an increase in hemoglobin, and in the total serum proteins, and in sigmoidoscopic and roentgenologic evidence of improvement in the diseased portion of the bowel.

A remission was induced in eleven out of twelve patients, nine of whom are still in remission after periods varying from two to twelve months. A relapse has occurred in two patients, in one after seven, and in another after nine months of freedom from the symptoms of colitis. A remission has again been induced in each of the two. The eleven improved patients are at present engaged in useful activity or gainful employment.

FRANZ J. LUST

PANCREAS

DAVIES, J. N. P.: *The essential pathology of Kwashiorkor.* (Lancet, V. 254, p. 317, Feb. 28, 1948).

Kwashiorkor is a disease very prevalent among African natives. Probably every African child has this disease in a more or less moderate form. It is found in its severest form in patients with malnutrition and possibly is intensified by malaria. Every case coming to autopsy shows some degree of pancreatic fibrosis. Pot-belly and steatorrhea are common findings. Meat fibers are not well digested. In consequence of the pancreatic malfunction the liver becomes infiltrated with fat. If the patient survives, the fatty infiltration disappears but there is no clinical improvement. An analogy is drawn between Kwashiorkor and the Anderson-Farber syndrome. Davies believes that pancreatic insufficiency may be a factor in the high mortality of African natives from respiratory infections.

LIVER AND GALLBLADDER

LEVY, L. K. AND BURCH, G. E.: *Studies of venous pressure in hepatic cirrhosis.* (Ann. Int. Med., August 1948, V. 29, No. 2, 274-277).

Ten patients with obvious hepatic cirrhosis were studied using ten normal controls. Venous pressures were read in the antecubital veins, the superficial abdominal group of veins and the veins of the dorsal rete of the foot, prior to and at once following paracentesis. A wide range of variations in the values for venous pressure were found, with overlapping of values for normal and abnormal subjects. Paracentesis produced a slight fall of pressure in the abdominal veins. The results were too inconsistent to permit use of venous pressure determinations as reliable diagnostic evidence in suspected cases of cirrhosis of the liver. The investigation, however,

demonstrated the value of paracentesis in improving the hemodynamics of the venous circulation below the level of the diaphragm.

LJUNG, O.: *The diagnostic value of the bilirubin excretion test in dubious cases of icterus.* (Nordisk Med., Aug. 6, 1948, V. 39, No. 32, 1456-1459).

In dubious cases of jaundice, particularly in those where the question of differential diagnosis between liver dysfunction and hepatitis or cirrhosis has to be settled, a high percentage of bilirubin retention is no evidence of the presence of the latter, more serious conditions, but seems rather to indicate a liver dysfunction. In 17 cases of dysfunction ("non-hemolytic hyperbilirubinemia without direct van den Bergh reaction") the bilirubin retention was higher, i. e., more than 40 per cent, than in 22 cases of subacute hepatitis, while in 12 patients with cirrhosis or chronic hepatitis, the percentage of bilirubin retention was higher than 40 per cent in only four.

ULCER

BALL, ROBERT P., SEGAL, ALLAN L. AND GOLDEN, ROSS.: *Post bulbar ulcer of the duodenum.* (Am. J. Roentgen. and Radium Th. 59, 1, 90. January 1948).

Ulcers of the duodenum located distal to the bulb show a smooth, rounded indentation of the wall at the level of the crater with an eccentric narrowing in all cases examined. Evidence of mechanical obstruction has not been found in the present series of cases. Enlarged, distorted mucosal folds, irritability of the bulb and hypermotility are associated findings. The ulcer crater is not always seen.

The use of exaggerated oblique projections with the patient in horizontal position or with the head lowered below the horizontal plane has been found to be helpful in disclosing the presence of post bulbar ulcer lesions. The actual incidence of post bulbar ulcer is difficult to evaluate. In cases with hemorrhage from the gastrointestinal tract, particularly in those cases associated with back pains and symptoms of peptic ulcer, the possibility of post bulbar ulcer should be seriously considered. The authors show the importance of the use of the "spot film" technique in the search for the ulcer.

FRANZ J. LUST

BRUUSGARD, CHRISTIAN: *The operative treatment of gastric and duodenal ulcer.* Acta chirurgica Scandinavia, V. 94, Suppl. 117. Oslo 1948).

This supplement fell only lately in our hands, but it is of such high quality that we like to draw the attention of our readers to this publication. The author calls it: a clinical and roentgenological study, however, it is more like a textbook, for it contains on 435 pages nearly one hundred roentgenograms and drawings. Besides there is an exhaustive bibliography. The author's material comes from different hospitals in Oslo, it includes approximately 1200 operative cases, demonstrating the immediate operative results, while 700 of the cases have been subjected to follow-up examinations and form the basis of the evaluation of the late results. The results are very good, but do not show any surprising results. The importance of the book lies in its excellent roentgenological examinations, which are explained by drawings of the surgical procedures. The different modifications of the two basic operations, gastrojejunostomy and gastric resection, are shown in these drawings and their roentgenological appearance is demonstrated. This is especially important for the non-surgeon.

Among the postoperative complications in the immediate course after gastrojejunostomy inhibited gastric evacuation was first in importance, occurring in 15%. The most grave retention in the form of gastric obstruction occurred in 2.4%, the rate of mortality being 1.2%. It is the author's opinion that a supplementary surgical procedure should not be postponed until the general condition of the patient is noticeably reduced. The incidence of postoperative hemorrhage was 2%.

For gastric resection the Billroth II method and its modifications has been used exclusively, it had a 4% mortality rate. Peritonitis was the most serious of the postoperative complications. It occurred in 17 of 578 operations, eleven with a fatal result. Postoperative gastric evacuation difficulties have been much less pronounced after resection than after gastrojejunostomy with an incidence of 5.9%. Postoperative hemorrhage occurred in 2%. The author's follow-up examinations support the conception that the presence of hydrochloric acid in the secretion of the postoperative stomach is of decisive importance in the occurrence of ulcerations in the stomach and anastomosis. Such ulcerations only rarely were seen in patients over 60 years. The postoperative complications after gastrojejunostomy are dominated by the prognostically serious recurrent ulcers, and by hemorrhage, while those after resection are dominated by the prognostically benign anemia. Gastritis occurs with the same incidence in both groups.

The author's material shows a cure after gastrojejunostomy of 63%, after gastric resection in 84%. If the anemias were not registered as not cured, the percentage of cure in the author's resection material would be 90%. In patients over 60 years of age, and preferably in cases of juxtapyloric ulcer, gastrojejunostomy will give equally satisfactory results as resection.

FRANZ J. LUST

SURGERY

Symposium on Appendicitis. (J. Indian Med. Assoc., May 1948, V. 17, No. 8, 251-266).

Some of the points of interest brought out by Indian surgeons and physicians in this symposium: In the older patients symptoms are less marked than in the young. Entameba may at times be the

causative organism. The removal of the appendix does not always bring permanent relief in so-called chronic cases because these are not cases of pure appendicitis but composite pictures in which other organs are involved. Treves, who popularized appendectomy by operating on King Edward VII saw his own daughter die of the disease before the surgeon could operate on her. The days when surgeons "were bred in the fear of the Lord and the peritoneum" are gone by, and the advances in surgery and chemotherapy have reduced the operative risk to practically zero. The problem as to whether "chronic appendicitis" actually exists has not been settled. X-ray should have no place in the diagnosis of acute appendicitis, but is useful in the differential diagnosis of pain in the lower right quadrant.

DOUBILET, H. AND MULHOLLAND, J. H.: *Surgical treatment of recurrent acute pancreatitis by endocholedochal sphincterotomy.* (Surg. Gynecol, Obstet., V. 86, p. 295, March 1948).

The study was carried out by means of roentgenographs and kymograph recordings on patients with recurrent acute pancreatitis. The resistance of flow of bile into the duodenum is attributed to two components: the sphincter of Oddi and the duodenal musculature. Normal sphincter resistance is a constant factor which may be modified by emotional disturbances or by the acidity of the duodenum. The resistance of the duodenum is equal to 100 to 120 mm. water pressure and is increased by either raised intestinal tonus or passage of a peristaltic wave. If recurrent acute pancreatitis is due to reflux of bile because of stricture at the sphincter, then endocholedochal sphincterotomy is advocated as a necessary procedure.

EXPERIMENTAL MEDICINE

PHYSIOLOGY

BORCH-MADSEN, P.: *Absorption in experimentally induced achylia.* (Fors. Kobenhaven. Ber., V. 225, p. 322, 1946).

Hypochylia and achylia were produced in 11 pigs by partial resection of the fundus. Growth was normal and no pellagra was observed. The absorption of dry matter, fat, nitrogen, carbohydrate, calcium, and phosphorus was not reduced below the level found in normal pigs. Addition of vitamin D improved absorption in both the hypochylous pigs and normal pigs.

SEQUIN, F.: *Comparison of intestinal and rectal absorption of amino-pyrine in the rat.* (Rev. Canad. Biol. V. 6, p. 724, 1947).

Isolated intestinal and rectal loops in the rat were filled with aminopyrine and the amount of drug remaining in the loop after various time intervals was determined. Absorption was more rapid and at a more uniform rate from the intestinal loops.

PONOMANER, G. A.: *Influence of nicotinic acid on rates of absorption and elimination of some sulfonamides.* (Farmakol. i Toksikol., V. 10. p. 16, 1947).

Sulfanilylcyanamide and sulfadiazine were given to rats by stomach tube. The addition of nicotinic acid increased the absorption of the sulfonamides from the gastrointestinal tract and also their excretion in the urine. Nicotinic acid given subcutaneously was not effective.

SCHWEINBURG, F., FRANK, E., SEGAL, A., AND FINE, J.: *Gaseous distension in the obstructed small intestine of cats.* (Proc. Soc. Exptl. Biol. Med., V. 66, p. 45, Oct. 1947).

Closed segments of the stomach and entire small intestine of cats were used. Gas formation was induced by malted milk and milk mixtures. Various sulfonamides and other antibiotics were given and the amount of gas formed then determined. Sulfadiazine, sulfamerazine, sulfamethazine, sulfathiazole and sulfathalidine depressed markedly the gas formation. Sulfasuccidine was less effective while phthalic and succinic acids were ineffective. In some experiments streptomycin inhibited gas formation but not in others. The drug which was most effective of all those tested was found to be penicillin.

AUER, J. AND KRUEGER, H.: *Experimental study of antiperistaltic and peristaltic motor and inhibitory phenomena.* (Am. J. Physiol., V. 148, p. 350, 1947).

This study was carried out on the descending colon of rabbits anesthetized with sodium barbital. Peristaltic and antiperistaltic waves of contraction are each preceded by a wave of relaxation. When the inhibition or relaxation wave passes over an area of colon, that area becomes relatively refractory to stimuli. The antiperistaltic as well as the peristaltic waves could pass without delay across a transverse incision which separated the colon by 60 per cent. Occasionally a peristaltic wave would traverse a complete incision of the colon but never an antiperistaltic wave or a wave of inhibition. Antiperistalsis was of central origin since it was abolished by destroying the central nervous system. In such cases the peristalsis, however, persisted. The authors obtained new evidence to show that during contraction of the longitudinal muscle layer there was a reciprocal inhibition of the circular layer and vice versa.

BEGTRUP, H. AND FOGE-HANSEN, E.: *Studies on plasma prothrombin following pancreatectomy.* (Acta. physiol. Scand., V. 14, p. 189, Sept. 1947).

Following pancreatectomy in dogs there is a decrease in prothrombin values. This decrease is not attributed to poor absorption of Vitamin K since this was given in water-soluble form. The prothrombin does not disappear altogether but it is only lowered, therefore prothrombin must be formed in the absence of the pancreas. The fatty infiltration of the liver resulting from pancreatectomy may be responsible for faulty prothrombin production in the liver.

Significant Factors in the Causation of Biliary Cirrhosis

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and

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BECAUSE BILIARY CIRRHOSIS is relatively rare in relation to cirrhosis in general, a study of our proven cases seemed to be desirable. All such autopsied cases from 1928 to 1945 inclusively at the State of Wisconsin General Hospital and University of Wisconsin Medical School were included. During this 18 year period 3922 post mortem examinations were done of which 2545 were males and 1377 females — a ratio of 1.85 to 1.0. The average age excluding those of one month of age or less, was 46.0 years. In this group 93 cases (2.38%) have been classified as biliary cirrhosis. This rate is slightly greater than that given by Karsner who reported an incidence of 2.0% in 1075 autopsies (1). There were 64 males and 29 females in this series, a ratio of 2.2 to 1.0. Correcting for the difference in sex of the entire series, the ratio becomes 1.18 males to 1.0 females.

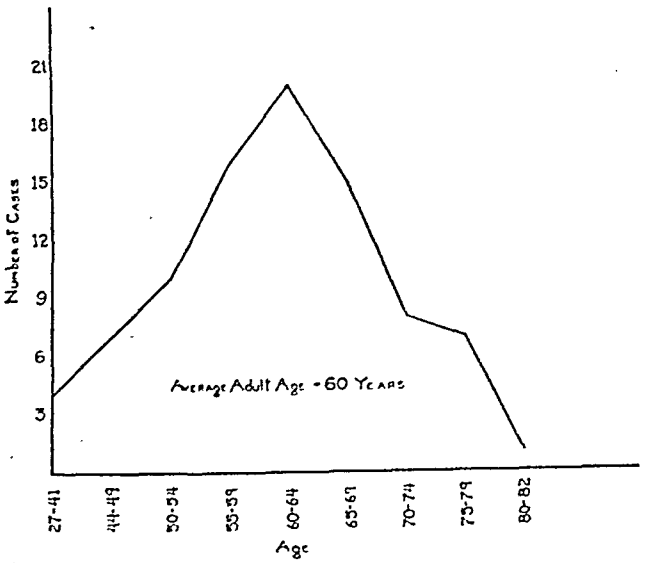


Fig. 1. — The distribution of adult cases according to age

The histological sections from cases of biliary cirroses were reviewed and divided into either mild, moderate, or severe categories (Figs. 2, 3, and 4). Those with only minimal amounts of periportal fibrosis and slight proliferation of bile ducts with evidence of some bile stasis were considered as mild. When the lesions were conspicuous, and evidence of biliary obstruction was more extensive, they were classified as moderate. When fibrosis was extensive with marked evidence of biliary obstruction, the lesions were considered to be severe. These categories serve as a rough guide only since in most instances only one section of liver was available for evaluation.

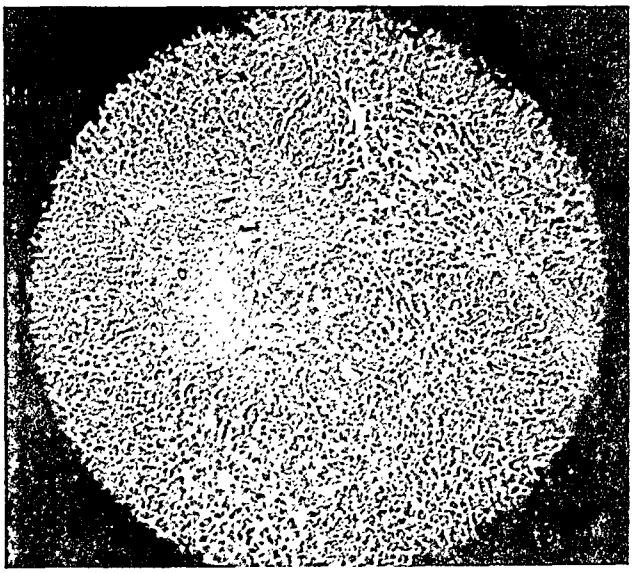


Fig. 2. — Representative section of liver from a patient with a mild degree of cirrhosis to show minimal periportal fibrosis

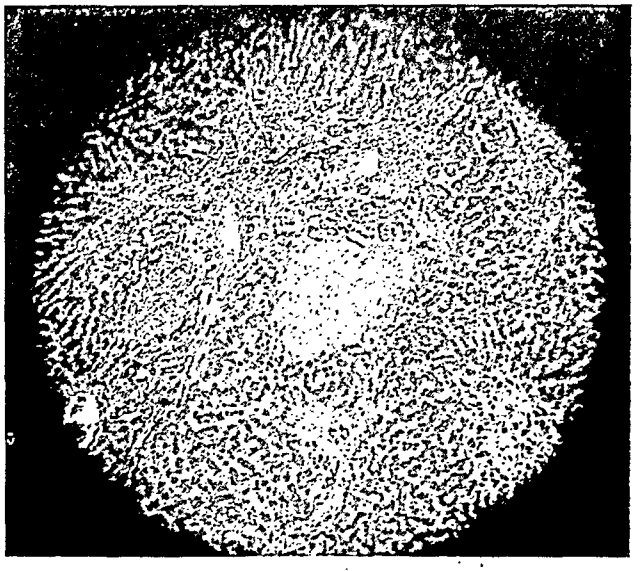


Fig. 3. — Periportal fibrosis is more extensive and there is a central area of necrosis. This is considered to be moderate cirrhosis

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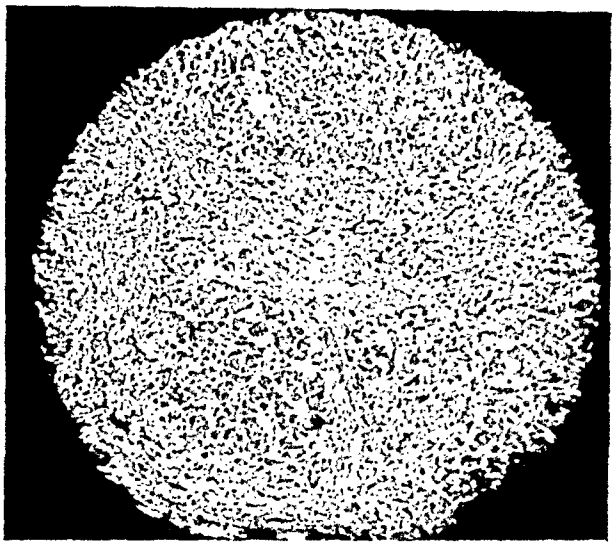


Fig. 4. — Extensive periportal fibrosis with considerable amount of duct proliferation in a liver with severe cirrhosis

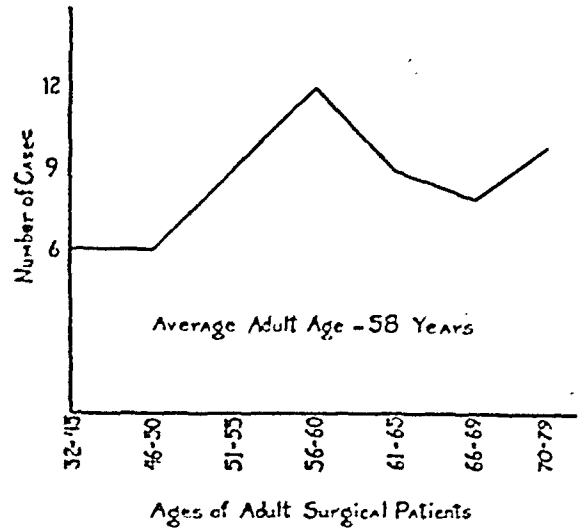


Fig. 5. — Distribution of surgical patients according to age

The incidence of various causes of biliary cirrhosis is given in Table I.

Carcinoma of the pancreas was the commonest cause of biliary cirrhosis by virtue of obstruction of the extra hepatic ducts. There were 23 males and four females. The majority of severe lesions, or 52.6% occurred in this group.

Pain was a common complaint as was weakness, vomiting, weight loss, and dyspnea on exertion. The average duration of jaundice was 10.4 weeks. Hematemesis occurred in two patients, one of whom had ascites. Pruritus occurred in 44.5% of these cases, all of which were in the moderate or severe histologic categories. Only 50% of the patients with severe lesions experienced itching. The average length of jaundice in these cases of pruritus was 16.2 weeks.

The largest liver in this group weighed 3620 grams, and the large size was attributable to abscesses. Two cases had enlargement of both spleen and liver. The largest number of cases (8) with ascites occurred in this group. Pancreatic fibrosis occurred in 44.5%

Gallstones in the common duct was the next most frequent cause of biliary cirrhosis — accounting for 21.5% of the total. There were 11 males and nine females (a ratio of 1.2 males to 1.0 female). Correcting for the post mortem room population, however, it becomes two males to three females.

TABLE I

	Incidence		Average age in years	Range of ages in years	Mild	Moderate	Severe	Average duration of jaundice in weeks	Number of cases with ascites	Splenomegaly	Hepatomegaly	Number of cases with cholelithiasis	Number of cases with pancreatic fibrosis
	No.	%											
Carcinoma of pancreas	27	29.0	60.4	45-79	9	8	10	10.4	8	3	5	5	12
Stone in common duct	20	21.5	58.5	16-79	8	9	3	6.5	2	7	4	20	13
Carcinoma of bile ducts	16	17.4	63.6	34-79	6	9	1	11.2	2	3	11	5	10
Carcinoma of gall bladder	12	12.9	63.8	49-79	5	7	-	7.0	1	4	7	9	10
Pressure on common duct	7	7.5	45.7	7-75	3	4	-	9.6	2	3	4	1	2
Stricture of common duct	5	5.4	50.8	41-68	-	4	1	-	1	2	3	-	3
Congenital atresia of bile ducts	3	3.2			-	-	3	-	1	3	3	-	-
Hepatic carcinoma	2	2.1			-	2	-	-	1	1	1	-	1
Chronic hepatitis	1	1.1			-	-	1	-	-	1	-	1	-
Totals	93				31	43	19		19	27	38	41	51

Abdominal pain was the most common complaint. It was present in 80% of these patients. Other common symptoms were chills, fever (Charcot type), flatulence, fatty food intolerance, nausea, vomiting, constipation, diarrhea, and dyspnea on exertion. Only one patient had hematemesis and one had hematuria. The jaundice was not so severe nor of such long duration as that of the preceding group. A history of pruritus was elicited in seven or 35.0% of the cases. As in the above group, only moderate and severe degrees of cirrhosis appeared in these patients. Likewise these cases comprised 58.0% of the 12 moderately and severely damaged livers.

The largest liver weighed 2600 grams, and it was without abscesses. The largest number of liver abscesses — three cases — occurred in this group. group. In two instances there were both enlarged livers and spleens; neither had ascites. The largest number of cases with splenomegaly (over 250 grams) occurred in this group. It is of interest that pancreatic fibrosis occurred in 65.0% of these cases.

Carcinoma of the bile ducts accounted for 17.4% of the cases. Males predominated in this small group by 4.4 to 1.0.

Pain was not such a common symptom in this group but did occur in 50% of the cases. Weakness and weight loss were uppermost on the list. Pruritus was present in 56% of these patients. The average period of jaundice in the pruritic patients was 15.2 weeks as compared with 11.4 weeks for this entire group.

Multiple liver abscesses were present in one case with cholelithiasis. The largest number of cases with livers of over 2000 grams occurred in this group. Varying degrees of pancreatic fibrosis occurred in 62.5% of the cases.

Carcinoma of the gall bladder accounted for 12.9% of the entire series. This was one of the few groups in which the females exceeded the males by two to one. This ratio becomes even more significant when one corrects for the post mortem population.

Pain was again a common complaint. There were five cases with a bleeding tendency such as: hematuria, epistaxis, petechial hemorrhage, purpura, and hematemesis.

Cholelithiasis was found in 75% of this group. No stones were found in the common duct. There were no liver abscesses. Pancreatic fibrosis occurred in 83.5% of the cases.

Presure on the common duct due to tumors about the bile ducts, often with metastasis in the area as well as in the liver was responsible for the obstruction in the majority of cases. A young patient with a large liver abscess accounted for another. All the patients (7) were males.

This group was composed of three cases of carcinoma of the stomach, one of carcinoma of the esophagus, an intra-abdominal myosarcoma, a large liver abscess, and a sympathicoblastoma in the right lumbar ganglion in a seven year old boy.

Pancreatic fibrosis occurred in two cases.

Stricture of the common duct accounted for five of the 93 cases. As one would suspect, the females predominated in this group.

One patient gave a history of cholelithiasis and a cholecystectomy four years before death. An exploratory laparotomy one year and seven months prior to death revealed marked adhesions about the gall bladder with almost complete stenosis of the common duct.

A second case gave a history of a cholecystotomy and removal of a stone from the gall bladder 11 months before expiration. A cholecystectomy done 16 days ante mortem revealed a stricture of the common duct.

The third case gave a history of a cholecystotomy, a cholecystectomy, and a right nephrectomy at 31, 21, and 17 years previously. An exploratory laparotomy revealed extensive adhesions about the gall bladder bed and ducts.

The last case was operated upon nine days before expiration. There was a stricture of the common duct. Autopsy revealed chronic choledochitis, obstructing granulation tissue, and a congenitally cystic left duct.

The remaining case of this group was not treated surgically. Autopsy revealed cholecystitis, hepatitis, and acute choledochitis.

Congenital atresia of the bile ducts accounted for three cases. One had atresia of the bile ducts; one a congenital stricture of the common duct; and one had congenital anomalies of the bile ducts with absence of the cystic duct, abnormal union of hepatic and pancreatic ducts and an atresia of the duct of Wirsung. The liver lesions of all three were classed as severe.

There were 12 cases of primary hepatic carcinoma encountered in the 3922 autopsies. This figure coincides with that of Karsner's (1) who reported an incidence of 0.3%. Of these 12 cases two had biliary cirrhosis. Others have also reported this same lesion in hepatic carcinoma (3). The degree of cirrhosis was classed as severe and moderate. Both patients were males, one aged 55 and the other 67 years.

The last case of the series is that of chronic hepatitis. The patient was a 65 year old man. He noted a constant jaundice for about six months and later developed pruritus. At operation a diagnosis of chronic hepatitis, chronic cholecystitis, cholelithiasis was made. The icterus index never exceeded 30.

DISCUSSION

Somewhat over 80% of all our cases of biliary cirrhosis had four groups of etiologic background: (1) carcinoma of the pancreas, (2) stones in the common duct, (3) malignant tumors of the bile ducts, (4) and neoplasms of the gall bladder. The average

age of the patients with malignant lesions was 60.7 years. Malignant lesions were responsible for 63 cases (67.8%) of the total. Of these, 49 occurred in males and 14 in females — a ratio of 3.5 males to 1 female. Correcting for sex, this ratio becomes 1.89 to 1. Thus the males accounted for 77.8% of all the neoplasms in this series. Likewise carcinoma of the gall bladder and the pancreas accounted for 12 or 85.8% of the malignant neoplasms in women. Of all the malignant tumors of the pancreas, gall bladder, bile ducts, and liver that occurred in the 3922 autopsies, 56.0% produced obstructive cirrhosis.

The incidence of carcinoma of the pancreas in the entire series of hospital necropsies was 1.7% (or 67 cases). This lesion accounted for 27 of the 63 cases of neoplasms in this study. Thus 40.4% of all the cases of malignancies of the pancreas that came to post mortem had developed obstructive cirrhosis.

Of the 63 tumors in this series, 30 cases occurred outside of the biliary system and 33 cases within. Carcinoma of the bile ducts comprised 25.4%, and neoplasms of the gall bladder 19% of the malignant lesions in this series. Again, 48% of all the carcinomas of the gall bladder that came to autopsy in this period of 18 years developed obstructive cirrhosis of the liver. Females predominated in this latter group. This lesion was responsible for 57% of all the malignancies that produced biliary cirrhosis in this sex.

The non-neoplastic group accounted for about one-third of the 93 cases. The incidence of males and females was equal (15 and 15). The average age, excluding the three cases of congenital atresia, was 55.6 years. Two-thirds of these cases were due to stones in the common duct. Of 460 cases of cholelithiasis found in 3922 autopsies, 4.35% had obstructive cirrhosis. The incidence of gallstones in the entire post mortem series was 11.6%; whereas the rate of occurrence in the selected 93 cases amounted to 47.4% or 41 cases — a frequency four times as great. Significant also was the finding that 75% of the cases of neoplasms of the gall bladder had an associated cholelithiasis.

Although it is conventionally thought that jaundice occurred in 100% of all cases of obstructive cirrhosis, six of 93 cases were anicteric. The degree of liver involvement in these cases was mild. There were, however, two cases with a moderate degree of cirrhosis. One patient died in a bus terminal, and autopsy revealed carcinoma of the bile ducts. Two cases of adenocarcinoma of the gall bladder were in this group. One of these patients had "white stools" about a week before death. A fourth patient, had an adenocarcinoma of the stomach with metastases to regional lymph nodes. Bile pigment in the urine was present in a dilution of 1:60. He looked "sallow" on physical examination. No icterus index was obtained, and no note was made about the color of the skin at autopsy. Another male gave a history of "slight if any jaundice" prior to cholecystectomy about one year prior to death which was due to carcinoma of the pancreas. This last patient, who had a stone in the common duct, was noted to have a slight icterus on the 13th day ante mortem; but no further notations were made, not even at post mortem. An icterus index was not obtained. He gave a history of peptic ulcer and fatty food intolerance.

These six cases arouse one's curiosity. Were the histories given by the patients accurate? Were they adequately and accurately taken? Was the bile duct obstruction incomplete, or complete but with remissions at short intervals? Could one of the hepatic or smaller ducts have become occluded, resulting in a regional obstructive cirrhosis? Were the histological sections representative of the entire liver? Is the obstruction alone responsible for the biliary cirrhosis? How great a role did infection play in the formation of these lesions and yet produce no jaundice?

It is of interest that another small group of cases gave no history of jaundice, but became icteric during the last week or ten days of hospitalization. The highest icteric indices ranged from 30 to 125 units. These cases showed approximately the same degree of hepatic damage (three mild and three moderate). Moreover, histological sections from these cases revealed many areas of parenchymal cells that appeared almost normal. Infection may be a factor in the formation of the cirrhotic lesion (5). In some acute liver diseases where parenchymal damage is great, death may occur without jaundice (2). Some of the cases in this series showed little cirrhosis but conspicuous generalized destruction of parenchymal cells.

Duration of jaundice, in the entire series, was 10.2 weeks, and the average highest icteric index was 83. The group of 19 severe lesions had an average period of skin pigmentation of 15.8 weeks, the group of 43 moderate of 9.9 weeks, and the group of 31 mild 6.9 weeks. The average highest icterus indices were: severe 77, moderate 92.7, and mild 75.6. However, as one scans the various individual figures of these groups, he is impressed by the inability to predict the amount of liver damage by reason of duration and intensity of jaundice.

Jaundice, clay colored stools, and dark urine were by far the most common findings. Abdominal pain was next most frequent, occurring in 65 cases or 70%. Pruritus occurred in 42 or 45.1% of the cases. In two, the itching preceded the icterus. Most of the liver lesions of the patients with pruritus fell into the moderate and severe groups — 35 of the 42 or 83.4%. The duration of jaundice was 14 weeks, and the average highest icterus index was 86. The frequency of other symptoms was: dyspnea 37.6%, vomiting 34%, flatulence 31%, bleeding tendencies 29.7%, constipation 22.3%, diarrhea 13.8%, and headache 9.6%.

Hepatomegaly occurred in 40.8% of the cases. Enlargement of the spleen occurred in 16 cases or 42.1%.

Six of these 38 cases also had ascites. The combination of hepato-splenomegalia and ascites occurred in three cases. In 65 of the cases of the entire series the liver weighed over 1500 grams. The largest liver 3840 grams — was in a patient with a neoplasm of the gall bladder. Three livers weighed less than 1000 grams. These latter cases occurred in association with carcinoma of the pancreas. They weighed 760, 830, and 960 grams.

Splenomegaly occurred in 27 or 29% of the cases and only three of these had accompanying ascites. There were seven cases in which the spleen weighed less than 100 grams and only one had ascites.

Ascites occurred in 18 cases or 19.4%. There were only two cases in which the spleen and liver did not weigh more than 150 and 1500 grams respectively. Of the eight cases that occurred with carcinoma of the pancreas, none had hepatomegaly or splenomegaly. Hypoproteinemia may be a factor in the production of ascites, but there are other factors (4). Ten of the above 18 cases had records of protein determinations. In only two was the serum albumin below 3.0 grams.

Varying degrees of interlobular and interacinar pancreatic fibrosis occurred in 51 cases, or 55.0%.

Operations were performed on 55 of the 93 cases (59%). Of these 16.3% recovered uneventfully. In addition there were eight cases (not included in the series of 93 cases) that were treated surgically for biliary cirrhosis. Seven of the eight lived for a known period of 1.5 months to 3.5 years. Some are still living. The average age of the patients was 55.4 years. This includes three children aged three months, seven years, and 15 years. Of the 19 lesions classified as severe in this series 14 or 74% of them became surgical cases. Of the moderate and mild liver lesions, 53.3% and 58% respectively were among this group. Again one is reminded that the mild lesions of cirrhosis do not indicate the degree of liver cell damage.

Obviously the prognosis of the majority of these patients with liver cirrhosis, whether or not surgery is attempted, is poor. Surgery was done frequently as a palliative procedure. Then too, the above figures do not include cases of simple obstructive jaundice but only those whose liver is damaged sufficiently to have gone on to biliary cirrhosis.

The immediate causes of death of the 93 cases were: 30 cases with bronchopneumonia, 16 with peritonitis, and eight with a combination of both. There were 13 cases with terminal hemorrhage, five of whom also had bronchopneumonia. Uremia and renal failure accounted for nine terminal events, four of which had bronchopneumonia and one with peritonitis and bronchopneumonia. One case had a coronary occlusion, two had septicemia, and one died in shock. There were 13 cases in which the immediate cause of death was undetermined.

SUMMARY

The main causes of biliary cirrhosis are: malignancies of the pancreas, gallstones in the common ducts, neoplasms of the bile ducts and gall bladder, pressure on the common duct for various reasons, stricture of the common duct, and congenital atresia of the biliary ducts. In 93 cases of biliary cirrhosis, the neoplastic lesions exceeded the non-neoplastic by 2.1 times, In the males 49 lesions were malignant and 15 benign, and in the females they were 14 and 15 respectively. Thus the females accounted for 50% of all the benign lesions and 32.2% of the neoplasms in this series.

An incidental but interesting finding was that the cases with splenomegaly, hepatomegaly, and ascites had an average duration of jaundice of exactly 12 weeks each, and the percentages of moderate and severe lesions were 70.5%, 71.7%, and 72.2% respectively.

In cases with splenomegaly, hepatomegaly, pruritus, and ascites, the one factor that was consistently above the mean was the average duration of icterus.

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Volume 16
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A Clinical Evaluation of Diverticulosis of the Colon

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DIVERTICULOSIS OF THE COLON is one of the most common benign lesions affecting the bowel. Although it occurs frequently, it is generally considered to produce few or no symptoms. In order to clarify the relationship between symptomatology and organic changes, a study of 205 cases of diverticulosis of the colon was made.

PATHOLOGY

Diverticula of the colon are protrusions of the mucosa through the muscular coat of the bowel. The sacs do not contain muscular tissue. Feldman and others described four stages in the development of diverticulosis. In the first stage, the colon shows a spastic narrowing, localized or extensive, with a serrated or ragged contour. In this stage there may be minute or no demonstrable sacculations. In the second stage the formed diverticula are visible. The diverticulum has a short neck, which is produced by the pinching of the mucosal sac as it herniates through the muscular coat. The third stage, consists of an inflammation of the bowel wall and the diverticula, resulting in a colitis and/or pericolitis, with thickening of the wall and narrowing of the lumen. As a result of this inflammatory process a mass may form, which produces varying degrees of stenosis. The inflammatory process markedly distorts the diverticula.

Incidence: The incidence of diverticulosis of the colon varies considerably. The roentgen incidence ranges from five to 10 per cent.

Sex: There is a preponderance of males with this condition. Although there is no anatomic reason for the greater prevalence in males, it might possibly be due to the fact that males indulge in more strenuous physical activities. In our 205 cases, 118 were males and 87 females.

Age: The age of the patient seems to play an etiologic role in the formation of diverticulosis. Diverticulosis of the colon occurs at all ages but is most often seen between the ages of fifty and eighty years. Of the 205 cases, 163 or 79.5 per cent occurred between these ages. It was most common in the sixth decade. It occurred under the age of thirty in only two instances.

WEIGHT AND BUILD OF PATIENT

Many investigators believe that the weight and build of the patient is an etiologic factor bearing upon the frequency of diverticulosis. Although a large percentage of patients are of the short, well nourished, overweight, and stocky type, the condition is also often observed in slender and undernourished people. It is believed, however, that obesity plays a role as a predisposing factor. According to Roberts, every pot-bellied individual over sixty is likely to have multiple diverticulosis of the colon. Our studies do not show a greater preponderance of this condition in obese patients. Of the 205 cases, the record of weight and build was carefully observed in 70; of these, 18 were classified as obese, 40 were of medium build, and 12 were slender.

SYMPTOMS

There seems to be differences of opinion whether uncomplicated diverticulosis of the colon is responsible for the production of bowel symptoms. Lynch believes that all people with diverticulosis have some symptoms but these are overlooked or considered to be due to dietary indiscretions. According to Telling, symptoms are observed in 60 per cent of cases. It is our belief that bowel symptoms frequently occur secondarily, at one time or another, during the life cycle of diverticulosis, depending upon the stage and associated conditions. Since there are controversial opinions as to whether diverticulosis of the colon produces symptoms, a review of 205 cases of all stages was undertaken to determine the clinical aspects of this condition. A detailed study of symptoms, signs, bowel habits, and roentgen studies were made.

Bowel habits: There have been but few studies made of the bowel habits in diverticulosis of the colon. In order to ascertain whether diverticulosis was responsible for symptoms, it was essential to determine not only the bowel habits but bowel changes as shown in the stool examinations. It was thought that perhaps this correlation may be important, since the findings may have some bearing upon clinical patterns caused by diverticulosis.

Of the 205 cases, bowel habits were recorded as follows: 59 were normal, 92 complained of constipation, 15 alternating constipation and diarrhea and 39 diarrhea. Attention must be drawn to the fact that bowel symptoms may be intermittent, vague, or entirely absent. The bowel symptoms depend in a large measure on the stage of the diverticulosis and the secondary changes, such as, spasm, irritability and inflammation, which frequently accompany diverticulosis. The dura-

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tion of the bowel symptoms varies considerably but the symptoms are usually of short duration. Often there are no bowel symptoms, while in some cases there are episodes, either mild or severe in character.

Stools: It is not always possible to obtain a history of the type of stool. Of the 205 cases of diverticulosis, the formation and type of stools were recorded in 56, excluding those with diarrhea. The stools were normal in 24, formed but small in 15, soft and mushy in seven, and broken into small scybala (spastic type) in 10. It is interesting to point out that in the diarrhea cases, it was not a true form of diarrhea or watery stool but rather frequent movements of a soft mushy consistency expelled in small pieces. This type of stool is frequently encountered in cases of markedly irritable or unstable colons. The color of the stools in the 56 recorded cases was as follows: brown in 46, light yellow in nine, and grayish in one.

Blood in stools: in 99 of the 205 cases in which a record was made of the examination of the stools for blood; 72 revealed no blood, 13 occult blood and in 14 visible blood was detected. When blood is found in the stools, it should not be interpreted that it is the result of uncomplicated diverticulosis. It is essential that other explanations or causes for its appearance be considered, since blood is not usually found in the stools in uncomplicated diverticulosis of the colon. However, blood may be observed in cases with inflammation, erosion or secondary ulceration of the bowel. In the 27 cases revealing blood in the stools, 16 were the result of peptic ulcer and two of carcinoma of the colon. The presence of blood in the stools in uncomplicated diverticulosis is usually due to coexisting pathology elsewhere in the gastrointestinal tract.

Mucus in stools: The presence of mucus in the stools in cases of diverticulosis is not particularly significant since it is commonly noted in irritable, spastic colons. In 67 cases in which the stools were examined for mucus, 26 revealed varying amounts of mucus and in 41 cases no mucus was found.

Pain

Pain or abdominal cramps does not usually occur in uncomplicated diverticulosis of the colon. In many instances, pain may be due to a spastic colon secondary to diverticulosis. On the other hand, it is a frequent symptom in diverticulitis and other complications of diverticulosis. In 90 cases varying degrees of pain was recorded. The location was as follows: scattered over entire abdomen 10, upper abdomen 20, mid-abdomen 13, lower abdomen 20, left lower quadrant 15, right lower quadrant 5, left upper quadrant 7. In most of these cases the pain was unrelated to the diverticulosis.

Tenderness: In uncomplicated cases of diverticulosis the colon usually presents little or no sign of tenderness. However, owing to the frequent occurrence of spasticity and irritability of the colon, palpation may reveal a sensitive bowel. In 65 patients in whom signs of tenderness were recorded, 42 manifested tenderness in various parts of the abdomen. The tenderness was not often localized and was too vague in character to be significant.

Irritable spastic colon: An irritable spastic colon, segmental or diffuse, was frequently observed associated with uncomplicated as well as complicated diverticulosis. Of the 205 cases, an irritable spastic colon was observed roentgenologically in 130 cases or 63.4 per cent. The high incidence of irritable spastic colon associated with diverticulosis is significant and presumably must be considered as a possible causative factor in the production of symptoms.

Location of the diverticula: In the vast majority of cases the site of diverticula was in the sigmoid and pelvic colon. In our 205 cases 177 or 86.3 per cent involved the sigmoid and descending colon. Diverticulosis is rarely seen in the rectum and cecum but when it occurs in these segments, may be solitary.

Number of diverticula: The number of diverticula in the colon vary considerably. The diverticula sacculations are nearly always multiple. In 186 of the 205 cases the diverticula were numerous, in 12 cases a single diverticulum, and in seven two diverticula were observed.

Proctoscopic examination: A proctoscopic examination was made in 56 of the 205 cases. No significant rectal changes were observed.

Association of diverticula elsewhere in the digestive tract: Diverticula were found in other parts of the gastro-intestinal tract in 28 cases; 24 of these were in the duodenum and four were in the esophagus.

Complications: The complications of diverticulosis are diverticulitis, abscess, obstruction, peritonitis and fistulous formation. Diverticulitis is the chief complication of this condition. Its medical and surgical incidence varies considerably. In our series of 205 ambulatory cases the roentgen signs of diverticulitis were observed 23 times or 11.2 per cent.

All cases of diverticulitis produce bowel symptoms. The severity of the symptoms varies. Flatulence and distention may be the only symptoms. Constipation is commonly observed and frequently it alternates with diarrhea. There may be acute attacks of pain, tenderness, with muscular rigidity on the left side, characterized by remissions and exacerbations. The stools may show evidence of blood. According to Spriggs, blood is found in the stools in five per cent of cases of diverticulitis. A tumor mass may be noted in diverticulitis. It is usually small in size but in rare instances it may be quite large. One of the characteristics of the tumor is its variability in size, decreasing during a quiescent period and reappearing during flare-ups of the condition.

Other complications: Obstruction was encountered in one instance. In one case perforation occurred.

There were no instances of fistulous formation among our cases.

Association with cancer: Cancer and diverticulosis coexist in about 1.5 per cent of cases. This association is a coincidence rather than a complication. Among our 205 cases, two instances of carcinoma were found, one involving the sigmoid, and one the ascending colon.

COMMENT

Uncomplicated diverticulosis of the colon does not as a rule produce intestinal symptoms. It is often associated with a spastic, irritable colon, which may produce some bowel symptoms, such as constipation or frequency of movements, small narrow stools, etc. Thus, since the irritable spastic colon is present at one time or another in a large percentage of cases of diverticulosis, it seems reasonable to suppose that the presence of an unstable colon does at some time produce bowel symptoms.

Diverticula sacs are pouches of mucosa without muscle tissue. Because of the retention of fecal contents, the diverticula and surrounding tissue frequently become inflamed. Just how often this occurs cannot be determined, but it probably occurs frequently enough to account for symptoms in many patients. There seems to be no question that secondary transient mild inflammation of the bowel, which spontaneously disappears, may account for frequent bowel episodes in diverticulosis.

Patients with uncomplicated diverticulosis often complain of bowel disturbance. Frequently it is mild in nature, due to a slight inflammatory involvement of one or more segments of the colon. There may be recurrent abdominal discomfort on the left side, associated with either constipation or loose stools, subsiding in a few days. In these cases the objective signs of diverticulitis are not usually demonstrable.

The suggestion is made that since irritable spastic colons are so frequently present in the series of cases reported, that it is conceivable that the diverticula present would tend to increase bowel irritability rather than serve as innocuous pouches. Certainly as we study these cases over a long period we are impressed with the frequent association of the two conditions. Thus, we offer the view that they are mutually disturbing in the sense that their association leads to more frequent symptoms, often mild in nature, in the absence of true diverticulitis.

SUMMARY

A clinical study of 205 cases of ambulatory patients with diverticulosis of the colon was made to determine whether uncomplicated diverticulosis is responsible for bowel symptoms. The vast majority of cases of diverticulosis of the colon do not present clinical manifestations. However, it is likely that mild bowel disturbances may occur at one time or another during the life cycle of diverticulosis as a result of associated conditions. Just how often these symptoms occur in uncomplicated diverticulosis remains undetermined.

Obesity was not a significant factor in the etiologic role of diverticulosis. Recurrent and intermittent disordered bowel habits was a frequent finding, but this was due to secondary conditions such as hyperirritability, spasm, or slight mucosal inflammation. The presence of mucus in the stools was observed in a large percentage of cases. This undoubtedly is due to the associated irritable, unstable colon. Of particular interest was the high incidence of the association of an irritable colon with uncomplicated diverticulosis. This may be a causative factor producing bowel symptoms. The cases with pain and tenderness encountered among this series of diverticulosis, could not be attributed to this condition, for in most instances it was unrelated to the diverticulosis. Diverticulitis occurred in 23 cases (11.2 per cent) and carcinoma in two instances. In our 205 cases of diverticulosis of the colon, diverticula were found in other parts of the gastrointestinal tract 28 times.

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Clinical Aspects of Prolapsed Gastric Mucosa

By

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THE CLINICAL ENTITY of prolapse of redundant gastric mucosal folds through the pylorus was first recorded by von Schmieden (1) in 1911 when he reported one case. No further recognition was given the condition until Eliason and Wright (2) described a single case in 1925. Reports of isolated cases followed. The literature was reviewed by Melamed and Hiller (3) in 1943 and was found to include 19 cases. After this time the condition was more widely recognized and more cases reported (4) (5). An excellent study of the condition and a report of 14 cases was made by Scott (6) in 1946. More recent reports were those of Nygaard and Lewitan (7) and Bralow and Spellberg (8). Scott (9) recently X-rayed approximately 250 patients without gastrointestinal complaints and found prolapsed gastric mucosa in none.

INCIDENCE

For many years prolapse of redundant folds of the gastric mucosa through the pyloric canal was thought to be rare, but more careful search for and recognition of the condition suggests that is not infrequent. Rees (10) diagnosed the condition four times in 3,000 cases, an incidence of 0.13%. It should be pointed out, however, that all four cases were operated on. Scott (6) reported an incidence of 1.04% of gastrointestinal lesions. Of 10,500 general admissions at this hospital, the condition was diagnosed 25 times. This represents an incidence of 0.24% of all general admission and 1.0% of 2,511 X-ray examinations of the upper gastrointestinal tract.

We believe that our studies of the age incidence (Table I) are misleading as applied to the population in general; because all our patients are veterans.

TABLE I

Age groups	Number of cases	
	McKinney	Scott
20-29	7	4
30-39	8	7
40-49	3	3
50-59	5	0
60	2	0

This factor would tend to explain the apparent lowered incidence in the 40-49 age group in that this group tended to be too young for World War I and too old for World War II. There is a parallel, however, between our group and that of Scott (6) in that most cases fell into the age group 20-39 with actual peak occurring in the group 30-39.

All of the patients in this series were males; however, this is not surprising because the vast majority of patients in this hospital are males. Judging from such reports as those of Rees (10) and Nygaard and Lewitan (7), one must assume that the condition is by no means limited to males.

ETIOLOGY

Several theories have been advanced as to the etiology of prolapsed gastric mucosa. Eliason and Wright (2) theorized that the condition was the result of local hypertrophy caused by chronic, low-grade inflammation. Rees (10) noted that all four of his cases (at operation) had a narrowing of the pyloric lumen. He postulated that this resulted in hyperperistalsis of the stomach in an effort to force its contents through the smaller opening, and that this increased peristalsis resulted in a loosening of the attachment of the mucous membrane to the muscularis. It was the opinion of Scott (6) that the condition resulted from a structural defect which is inherent in all stomachs. This defect is in the stomach wall immediately proximal to the pylorus and is in the attachment of the mucosa to the muscularis at the region where there is a marked decrease in the size of the lumen of the stomach. He suggested that certain neurogenic factors are the inciting cause of a disturbed gastric function which ultimately brings about a mucosal prolapse.

We are willing to believe that any sessile mass in the proximity of the pylorus, whether it be polyp or hypertrophied fold, is apt to be swept through the pyloric canal and thus result in prolapsed gastric mucosa. Quigley (11) has shown that antral pressure is about 30 centimeters of water but may be as high as 90 centimeters. Narrowing of the pylorus is not necessary for the production of prolapse but is found in a few cases. We are inclined to believe that there is some individual predisposition to prolapse from an anatomical point of view since seven of our twenty-five patients showed abnormalities of the stomach other than prolapse. These included four cases of hiatus hernia, one of cascade stomach, one of high trans-

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verse stomach and one of gastric ulcer. One cannot deny that disturbed gastric function on a neurogenic basis may predispose to prolapse.

PATHOLOGY

The hypertrophied gastric folds show some hyperplasia of the glands of the mucosa; and the submucosa shows an increase in lymphocytes, plasma cells and eosinophils; however, the cellular infiltration is not clearly as prominent as it is in hypertrophic gastritis (6). Occasionally ulcerations or erosions are present on the folds, and at times these may bleed. Rubin (12) has reported *malignant changes in a prolapsed mucosal fold*; however, this was part of a generalized involvement of the gastric mucosa.

SYMPTOMATOLOGY

Certain symptom complexes are suggestive of this entity, but X-ray confirmation is essential to diagnosis. The following symptoms were most prominent in this series:

1. *Dyspepsia:* This may be manifested by pain, flatulence, heartburn, a sensation of fullness and/or nausea. This tends to occur after meals but usually lacks the regularity seen in peptic ulcer. Scott (6) and Rees (10) described dyspepsia in 100% of their patients. In our series of 25 patients, dyspepsia was definitely present in 20, was questionable or borderline in three and was absent in two. Of the two without dyspepsia, one was frankly psychotic and the other had esophageal varices.

2. *Absence of Night Pain:* In 17 of our patients checked for night pain, it was absent in 10, definitely present in two and highly questionable in five. This is an interesting point of distinction from peptic ulcer in which night pain may be a prominent feature.

3. *Vomiting:* Vomiting is not uncommon in this condition. It tends to be more frequent after heavy meals. It was present in 12 and absent in 12 in 24 of our 25 patients.

4. *Bleeding:* Gross gastrointestinal bleeding was present in seven of our twenty-five patients. Several had massive bleeding. It was absent in fifteen and questionable in three. Of these last three, one had esophageal varices, one had ulcerative colitis and one had persistent occult blood in the stool. None of these three are included in the seven described above.

The percentage of patients manifesting clinical bleeding in this series (28%) is quite comparable to the findings of Scott (21%), Nygaard and Lewitan (28%) and Melamed and Hiller (25%).

5. *Lack of Relief by Antacids:* Of our patients with dyspepsia, 29% obtained relief by the use of antacids while 71% received little or no relief. This is another clinical feature which may aid in differentiating prolapse from peptic ulcer.

6. *Relief by Food:* All of our patients with dyspepsia obtained relief from the taking of food.

7. *Associated Organic Disease of the Gastrointestinal tract:* This was present in seven of our patients and included hiatus hernia (four cases), esophageal varices (one case), gastric ulcer (one case) and ulcerative colitis (one case).

PHYSICAL EXAMINATION

The physical examination was usually negative but occasional cases did show epigastric tenderness on palpation.

X-ray: X-ray is essential in the diagnosis of prolapsed gastric mucosa. There is a typical deformity of the base of the duodenal bulb (See Figures 1. and 2.), caused by the mushroom-shaped mass of gastric mucosa which is extruded from the pyloric canal. In addition the mucosal folds usually can be seen in the pyloric canal extending from the antrum to the mass in the base of the duodenal bulb. The differential diag-



Fig. 1.



Fig. 2.

nosis of such X-ray findings rests between prolapsed antral polyp, duodenal polyp at the base of the bulb and pylyoric canal peptic ulcer with cicatricial deformity of the base of the bulb. The mucosal folds traversing the mass in the base of the bulb usually are not seen when the filling defect is due to a polyp. As a rule, pyloric canal ulcers do not cause a deformity of the bulb very suggestive of prolapsed mucosa. Duodenal ulcer is not very difficult to differentiate; because the ulcer tends to be located on the anterior or posterior wall of the bulb rather than on the base and thus tends to deform the entire bulb. Seen at fluoroscopy, a rapidly emptying or irritable bulb suggests duodenal ulcer or duodenitis. This "quick" or irritable bulb is not seen in uncomplicated prolapsed gastric mucosa. Finally, the fluoroscopic examination usually reveals increased gastric peristalsis, but as a rule there is no gastric dilatation.

Toward the end of the study of this series, the authors tried to reduce the prolapse in a few patients by external pressure during fluoroscopy. This idea was prompted by the history of one of our early patients who obtained relief from dyspepsia by leaning forward and applying external pressure to the right upper quadrant of his abdomen. The idea was furthered by the finding in one of Patterson's (13) patients at operation in whom the prolapsed mass was freely intermovable between stomach and duodenum. This reduction was attempted unsuccessfully on three of our patients at fluoroscopy; however, this study cannot be considered adequate because the number of patients on whom it was attempted was too small.

OTHER STUDIES

1. Gastric acidity is usually normal or low. Gastric analysis was done on nine of these patients. The degrees of free hydrochloric acid in the fasting specimens were as follows: 60-23-20-20-14-12-11-0-0. The one patient having hyperchlordydria was a 55 year old man who also had definite night pain.

2. Occult blood may or may not be present in the stool.

3. Blood and urine studies usually are normal unless there is active or recent bleeding from the prolapse.

4. Gastroscopy is usually negative, but occasionally large mucosal folds in the distal antrum may suggest the condition.

TREATMENT

Treatment may be medical or surgical. Surgical treatment is indicated if there is severe recurrent vomiting or severe recurrent hemorrhages. Conceivably, severe intractable pain may be an indication also. Two types of surgical correction have been recommended. These include partial resection of the stomach or excision of the prolapsed folds. None of our patients required surgery.

In general, medical treatment consists of diet and antispasmodics. Antacids seem to be of little or no value. The diet should be soft or liquid and should be given in multiple small feedings. In some patients, return to solid foods causes return of symptoms. In general, the response to this regimen was good; and so far as they have been followed, few have had recurrences. It should be stated, however, that our patients have not been followed for a long period of time. Several of our patients with hemorrhages required transfusion, and their treatment generally was that of bleeding peptic ulcer.

SUMMARY AND CONCLUSION

Certain clinical features are suggestive of the diagnosis of proplapsed gastric mucosa, but they are not consistent enough to make the diagnosis without X-ray confirmation. The salient features of the diagnosis in 25 patients are reviewed as follows:

(A.) Symptomatology: 1. Dyspepsia (80%) 2. Absence of night pain (59%) 3. Relief by food (100% of those with dyspepsia) 4. Little or no relief by antacids (71%) 5. Vomiting (50%) 6. Gross bleeding (28%) 7. Fairly common association with other organic disease of the gastrointestinal tract (28%).

(B.) Sparsity of physical findings.

(C.) X-ray findings: 1. Typical deformity of the base of the duodenal bulb. 2. Redundant folds through the pyloric canal. 3. The duodenal bulb is not irritable or "quick." 4. Increased gastric peristalsis. 5. Lack of gastric dilatation.

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Volume II
Number 1

Some Observations on Allergy of the Respiratory Tract

By

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IN THIS PRESENTATION, I shall include under the term "respiratory tract," all those organs which are concerned with respiration, the nasal cavities with their accessory sinuses, the naso-pharynx, the pharynx, the larynx, the trachea, the bronchi and the lungs. The reason is simple; because of their very close association, those conditions which affect one of these almost surely affects most, if not all of the others at the same time.

When we think of allergenic conditions in this area of the body, we naturally think first of that most obvious state, hay fever. Here we have an excellent example of a vasomotor rhinitis, involving the nose, the eyes and the pharynx, individually or collectively, and in varying degree. The nasal symptoms are the most annoying to the patient; in addition, disturbances of the pharynx, the palate and the ears are common and distressing.

The first nasal symptom is one of fullness and a gradually increasing obstruction to breathing; as the process progresses, the irritation induces repeated and protracted paroxysms of sneezing which may continue till the patient is exhausted. A profuse, serous, irritating discharge flows intermittently from the nose. Mouth breathing — a natural result of the nasal obstruction — disturbs the patient's sleep. Postnasal drip and headaches are frequent, the latter usually being caused by obstruction to drainage from the sinuses. Any or all of these symptoms, though primarily of allergenic origin, may be secondarily aggravated by such outside causes as temperature changes, draughts, certain odors, sunlight, chemicals and drugs, some foods, tobacco smoke and many others. These produce still further increase in the irritation to the already-afflicted mucous membranes of the respiratory regions.

PHYSICAL FINDINGS

The nasal mucous membrane will be pale and edematous. The turbinates will be swollen and usually bathed in a clear, watery secretion. Further, the mucous membrane, especially over the turbinates and in the lower nasal passages will be extremely vascular and contain large venous plexuses surrounded by fibres forming a species of erectile tissue.

In vasomotor rhinitis, there will be swelling of this erectile tissue over the turbinates, due to dilatation of the veins. The seasonal and perennial forms of this condition are also characterized by a persistent tendency to tumefaction of the inferior and middle turbinates.

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Typically, hay fever occurs periodically, due to the pollens of trees, grasses and plants. The pollenation season in this latitude usually begins in April, continuing through the growing months until October. Those individuals who are sensitive to the pollens of forsythia, birch, willow, maple, oak, elm and chestnut will display their symptoms through April and May. This is the smallest group. Those affected by the pollens of the grasses, timothy, red top, orchard grass and the like, are affected during June and July. Ragweed suffers, by far the largest group, are afflicted from about August 15th until well into October. Those who are allergic to more than one group of pollens, will of course, display symptoms over a longer period, sometimes covering the entire span from April to October.

PERENNIAL VASOMOTOR RHINITIS

Vasomotor rhinitis, other than that caused by pollens, that is, due to animal dandruff, chemicals or drugs, cosmetics or powders, foods, tobacco smoke and other substances, will display all the symptoms of the seasonal type but without reference to the time of year. In addition, the nasal disturbances may be unilateral, may change from one side to the other, may temporarily disappear altogether or re-appear on both sides at once. These patients, in addition to sneezing and nasal discharge, may complain of heaviness, dullness, inability to concentrate, loss of memory, nightmares and restless or broken sleep. Besides all this, the condition may become worse in the summer months, if the victim happens also to be sensitive to some of the pollens.

One allergen for this type of patient which is of especial interest is printers' ink. Used as it is in many items with which we all come into contact daily, newspapers, books, magazines and advertising matter, an allergy to it will be constantly in evidence. The symptoms are typical, sneezing, watery nasal discharge, stuffiness of the nasal cavities. It may affect the entire respiratory tract or any part of it; it may cause itching at the nasal orifices or on the skin of the face, lacrimation, itching of the conjunctiva of the eyes.

Printer's ink contains carbon black, violet toner and an oil base; the patient may be sensitive to any or all of these. Sometimes also, these inks have a most objectionable odor. On two different occasions in recent years — due perhaps to wartime difficulties in the publishing business — one of our medical journals smelled so badly that I was forced to lay it aside for a week before I could finish reading it.

The ink used in printing newspapers seems to be

the worst offender as a cause of allergic reactions, probably because it comes into our hands so much sooner after printing, when it is often literally "not dry from the presses," especially in damp or cold weather.

Though I hestitate to quote myself as a "case," I believe that my own reactions in this direction may prove illuminating. I have found that I myself am sensitive to newsprint ink; it causes itching of the nasal cavities and orifices and of the eyes and the skin of the face. The reaction is such that if I have read a paper in the evening, when I shave the next morning, I find small blisters on my face. I have tried covering the paper with cellophane, but found this hard on my eyes. Recently, my reactions seem to have lessened considerably; now I find that I can read for a short time, then go and wash my hands and face and blow my nose, after which I am able to go on reading again for a short time.

Some of my patients who are similarly affected have tried wearing a mask while reading. This works well enough apparently, but the masks do have to be washed or replaced rather frequently.

Case 1. Male age 21, technology student, first consulted me on January 10, 1922. He complained of sneezing throughout the year, which became worse between April and October. There were frequent attacks of asthma, obstruction and itching in the nasal passages, and eczema on the face, neck and other parts of the body. Cutaneous tests showed him to be sensitive to pollens prevalent throughout the April-October period as well as to certain foods. He was also hypersensitive to sunlight; exposure produced severe sunburn.

By avoiding the foods to which the tests had shown him to be sensitive, he was relieved of all his symptoms. However, in March of the same year, he complained of a return of the itching on his face and in his nose. One of the substances to which he had been shown to be sensitive was cocoanut oil. Unbeknown to him, a tradesman's error had added a nut margarine to his diet, containing this oil, which had been specifically forbidden to him by my diet restrictions. As soon as the error was discovered and corrected the symptoms disappeared again. At this time also, this patient was desensitized to his allergenic pollens; thereafter by adhering strictly to his diet, he was able to remain completely free of all symptoms of his perennial vasomotor rhinitis.

In connection with this case, it should be noted that patients who are sensitive to pollens will also be sensitive to some of the cereal grains. By avoiding these also, the patient will receive much greater benefit from pollen injections and obtain more complete freedom from all the symptoms of hay fever.

In addition to being relieved of his hay fever and other allergenic symptoms, it is gratifying to report that the patient referred to above, also seemed to lose entirely his excessive tendency to sunburn. Where previously he had not dared to go out without a hat, or in his shirtsleeves, he was able after treatment even to ride in an open car without protection from the sun, without untoward after effects.

The victims of vasomotor rhinitis frequently develop fissures at the angles of the alae nasal, these occurring with or without the presence of a discharge from the nose. Occasionally, these even become infected, producing localized abscess or cellulitus of the soft tissues with erythema of the cutaneous nasal surface

INTUMESCENT RHINITIS

In this condition, there is usually little if any excess of nasal discharge, though occasionally there is marked paresis of the muscular coats of the blood vessels and the muscular elements of the mucous membrane covering the turbinates and portions of the septum. This results in venous stasis and hyperemic swelling of these parts. When this occurs the patient's chief complaint is of obstruction to normal breathing from which there is no relief.

Case 2. Male, age 45, interior decorator, consulted me May 10, 1942. There was complete blocking of the nares; the patient never remembered being able to breath through his nose. During his working hours, the condition was worst. He had previously received many different forms of treatment including cauterization and surgery, but without obtaining relief. He suggested that I make test serums from some of the upholstering materials with which he had to work, but I told him those could not be the original cause of his condition as it was much older than his job. I did, however, make tests, with various foods, pollens, animal dandruff, etc., and prescribed a diet based on the findings. At this time, his nasal passages were completely blocked on both sides. Two weeks later, when he returned he expressed his condition as "one hundred per cent perfect . . . breathing through my nose!"

HYPERTROPHIC RHINITIS

This is a chronic congestion of the nasal mucous membrane which has led to a true connective tissue hyperplasia. The changes are chiefly localized on the inferior and middle turbinates and the septum, the membrane showing a slight general thickening.. The obstruction, though varying in degree with the individual case, is constantly present in contrast to that of vasomotor rhinitis, in which it may come and go.

While the seat of these abnormal swellings is most likely to be the posterior end of the inferior turbinate, hyperplasia of the middle turbinate is only slightly less frequent. However, in this case, a very different appearance is presented, the condition usually being confined to the lower border of the structure, and showing as a single, smooth translucent, edematous enlargement or as a group of polypoid protuberances suggesting a cluster of grapes. From these, it is but a step to the true nasal polypi.

NASAL POLYPI

When these formations are present, their mobility, translucence and the fact that a probe can move them back and forth and can be passed on either side of them, are adequate indications for diagnosis. Nasal polyps may give rise to no symptoms so long as they remain of small size; if large, however, they obstruct breathing, produce mechanical irritation and result in a discharge of a serous or purulent nature from the nasal mucous membrane.

These growths from the connective tissue of the

mucous surfaces may occur in great numbers in the nasal fossae and block these completely. In form, they may be either pedunculated or sessile and, in most cases, give rise to considerable discharge. It is probable that they result from chronic rhinitis and represent hyperplasia in a state of edema. Or they may result from irritation to the mucous surfaces which cause the latter to lose their normal smoothness, developing papillae, some of which, in turn, gradually develop into true polypi. Their growth is then favored by gravity and the edema caused by obstruction to return circulation through their stems. Such polyps have been found in persons of all ages; they are, however, rare in children and in the aged. They are most common in persons between twenty-five and fifty; there also seems to be an hereditary predisposition in some instances.

They are most often located on the lower border of the middle turbinate and in the middle meatus, although they may grow from any part of the mucous surfaces. Thus they may flourish in the ethmoid region, on the middle turbinate, the middle meatus, the upper turbinate and the upper meatus. They are also found attached to the edges of the hiatus semilunaris growing from the openings of the accessory sinuses or originating within the antrum of Highmore or the ethmoid cells. Though they are not the cause of reflex asthma, headaches, neuralgia, giddiness or congestion of the fauces, they do arise from the same factors which produce the latter.

Case 3. Male, age 35, consulted me, October 10, 1933. His complaint was of nasal obstruction resulting from polypi which developed so rapidly that they had had to be removed every two months for the past eight years. They had been removed six weeks before I saw him. I removed several at the time of the consultation and made a series of cutaneous tests for allergy. By following a prescribed diet and avoiding foods to which he was sensitive, he was relieved of the nasal obstruction, and no further polypi developed.

SINUSITIS

In conjunction with the various forms of vasomotor rhinitis there is frequently extension of the condition into the accessory sinuses, accompanied by edema of the nasal and sinus mucous membranes and discharge. Frequently the orifices of the sinuses become blocked, causing retention of these secretions within the sinuses, vascular paresis, pressure and pain. A fertile area is provided for the growth of various forms of bacteria. Under these conditions, roentgenograms may show different changes at different times in the same individual, these changes depending on the severity of the allergic reactions at the time of each examination.

Case 4. Male, age 30, was referred to me on August 10, 1929, because of asthma. A number of roentgenograms had been taken at different times by various X-ray specialists. One of these had given a definite diagnosis of sinusitis; another a week later, found no evidence to support his colleague, although the patient's asthma was equally severe at each time.

I have seen similar variations upon successive transilluminations of the sinuses, these being the same as those taking place in the nasal cavities in vasomotor rhinitis.

ATROPHIC RHINITIS

In this condition, the mucous membrane atrophies, the change being most marked over the turbinates. These shrink away leaving the nasal fossae abnormally roomy. At the same time, there occurs an extensive epithelial metaplasia from ciliated to pavement epithelium, making possible the adhesion of dried secretions to the mucous surface, in the form of crusts. The majority of these patients emit an offensive odor, a condition known as ozena.

If the accumulated crusts be lifted off, their under surfaces will be found to be moist or covered with fluid pus; it is from these that the offensive odor arises. These crusts may either be discrete or line the entire nasal cavity like a cast. The underlying mucous membrane is pale, but neither eroded nor ulcerated. In most cases, the patient will have lost his sense of smell — a mercy for him.

Atrophic rhinitis is the final stage of hypertrophic rhinitis. The patient becomes an object of disgust to others because of the stench he emits.

The secretion does not always consist of crusts. It may be semi-fluid-mucus, or muco-purulent or purulent in character.

The condition may involve the nasopharynx and the vault, these frequently being the seat of accumulations of dry scabs or semi-fluid pus.

Case 5. Female, age 55, consulted me on September 10, 1930, complaining of arthritis, gastro-intestinal distress and hypertension. She had had a radical antrum operation five years before, in an attempt to clear up a sinus condition. Vaccine had been made from the antrum pus, injections of which had been made in her leg. Infection had followed these, with serious results.

When I examined this patient, the characteristic foul odor was easily distinguishable five feet away. She stated that this had been the case ever since the operation.

Examination of her nose revealed large amounts of mucus, pus and crusts, and a very foul odor. Transillumination of the antrum was attempted, but no light came through. Cutaneous tests were made and a diet prescribed. By avoiding foods to which she had been shown to be allergic, she obtained complete relief. Not only were the odor and the mucus, pus and crusts eliminated, but also the other symptoms, hypertension, gastro-intestinal distress and arthritis, were completely relieved.

Case 6. Female, age 52, consulted me on April 6, 1932. This patient had large amounts of nasal discharge of mucus, muco-pus and pus. Crusts were present and a very offensive odor. She had lost her sense of smell. These symptoms had persisted for thirty years. She had consulted a number of rhinologists, received many kinds of treatment and gotten no beneficial results.

With this patient, as in the preceding case, all symptoms were completely relieved by the avoidance of foods to which she was allergic. Her only relapse occurred some three months after she consulted me, when she ate chocolate — one of her allergens — and showed a nasal discharge of large amounts of thick, gelatinous mucus within six hours.

ANOSMIA AND HYPEROSMIA

Essentially anosmia is due to the inhibition of function, the destruction or the atrophy of the branches of the olfactory nerve or of the olfactory cells and their supporting epithelium on the surface of the mucosa. Strong odors can cause total anosmia. Pus or crusts in the olfactory region can inhibit the sense of smell. The same can come about mechanically when the structures themselves are intact if the air currents are shut off by obstacles or the nasal fossae are much enlarged, as in atrophic rhinitis. For example, it may be possible to restore a sense of smell which has been absent for many years, by removal of a polypoid enlargement of the turbinates.

HYPEROSMIA

In different individuals, there are normally considerable differences in the acuity of the sense of smell. For this reason, its intensification can only be considered as pathological when it becomes an annoyance to the possessor. The condition may actually be one of increased irritability of the individual himself rather than one of extraordinary acuteness of perception of odors, when those which either do not disturb or are even pleasing to others, become disagreeable to him. For example, such persons may find the odors of certain flowers or drugs, or the smell of minute amounts of tobacco smoke intolerable.

These patients are not neurasthenic; they are simply allergic to the substances which produce their individual hyperosmias. Related disorders, such as headache, vomiting, palpitation, faintness and asthma, which occur concurrently, are also of allergenic origin.

PEROSMIA

This is a perversion of the sense of smell. It may be due to pathological changes within the structures of the nasal passages, or the nasopharyngeal and accessory sinuses. In cases five and six, above, the patients had lost their sense of smell, due to such pathologic changes in the air passages.

Case 7. Male, aged 48. This patient was sensitive to tobacco. He could detect the odor of tobacco smoke when it was quite unapparent to others.

Case 8. Male, aged 60. This patient's allergy was to perfume. He could detect the smallest amounts of it at a considerable distance.

ADENOIDS

Hypertrophy of adenoid tissue, though commonly seen in children, may appear in persons of any age who are afflicted with allergies. Hypertrophy of these tissues in the nasopharynx — adenoid growths — are frequently associated with enlargement of the faucial tonsils. These hypertrophic conditions occur so frequently in certain families that there seems little doubt that an hereditary factor is present in many instances.

In children affected with the nasopharyngeal changes, disturbed sleep and nightmares are frequent. These are due, not only to the actual difficulty in breathing and to the fact that the air is not properly warmed and moistened as it passes into the lungs, but also to allergenic reactions in the brain cells themselves.

NASOPHARYNGITIS

In this condition, swelling of the tissues, together with redness of the mucous membrane, are prominent features. This redness may vary all the way from the deepest hue to a scarcely-perceptible change in tint. The changes may be local or may involve the whole pharyngeal space; they may also involve the tonsillar faucial and pillars of faucial. There may be edema of the uvula; in some cases, the redness extends forward to include the soft palate and the roof of the mouth. Frequently there is lymphoid hyperplasia covered with mucus or muco-pus. The congestion may also extend down the post-pharyngeal wall to the larynx, with considerable edema of the inter-arytenoid area. There will also often be marked redness of the epiglottis especially along its margins. The post-pharyngeal region sometimes shows a glazed, reddened area; or it may appear as a marked hyperemia with lymphoid nodes or granulations over the surface. These hyperplasia may appear to be behind the posterior faucial pillars, looking like ridges, these extending from the nasopharynx down as far as the epiglottis. Some of these granulations may appear as blunt masses projecting slightly from the surface.

In this connection, it is essential to remember that the pharynx is unique in forming not only a portion of the upper air passages, but also of the digestive tract. This renders the mucous membrane of this area susceptible to any influences or conditions which affect the digestive tract. Thus disorders of digestion or assimilation are very apt to be accompanied by pathological changes in the pharynx. In an earlier paper (6) I called attention to the fact that in such systemic allergenic disturbances as arthritis, gastrointestinal disorders, dermatitis, headache, cardiac and vascular conditions, pathologic changes are frequently found also in the nares, nasopharynx, larynx and pharynx, these changes being produced by pollens and other air-borne allergens, foods or bacteria, and increased by irritating serous secretions. Involvement of the eustachian tubes may produce symptoms within the ear, such as itching, fullness, tinnitis and even deafness.

ANGIONEUROTIC EDEMA OF THE LARYNX

This is sometimes seen associated or alternating with attacks of urticaria. There may be simultaneous appearance of lesions on other mucous surfaces in the upper air passages. Even death, resulting from rapidly-progressing edema, has been reported. The swelling may persist for several days or may disappear in a few hours.

Case 9. Female, age 55, consulted me, April 10, 1934 because of frequent attacks of swelling and obstruction in the throat, obstructed breathing, cyanosis, these attacks continuing in severe form from four to twenty-four hours. The first such attack had occurred six months

before. Difficulty in breathing had been so severe that she had believed she would choke to death; with further increase in severity, her physician had referred her to me.

Among other things, I found the patient had an abscessed tonsil. This was removed and a suitable allergen-free diet prescribed. With the elimination of foods to which she was sensitive, the patient's symptoms were completely relieved.

LARYNGITIS

Acute laryngitis may occur as a result of inhaling various irritating substances, such as pollens in hay fever season. Bakers who inhale flour during working hours frequently become sensitive to it. Many substances can cause laryngitis in the allergic individual; drugs, chemicals, powders, animal emanations, tobacco or its smoke, perfume, and many others.

Case 11. Female, age 22, singer, consulted me on July 15, 1932. One year after graduating from the Conservatory of Music, she found that when she attempted to give an exhibition as soloist at a concert, her voice tired so rapidly she was not able to complete the recital. I made cutaneous tests and prescribed an allergen-free diet, after adopting which she not only was able to complete her commissions but was said to have improved in voice as well.

COUGH

Coughs of allergenic origin may be very slight or may be extremely severe with a loud ringing quality. The impulse may be sporadic or the attacks may be paroxysmal in character. At the beginning a cough is usually dry, but when kept up for a time, hyperemia of the bronchial mucous membranes gives rise to secretion. The irritation causing the cough is often referred by the patient to that part of the trachea located beneath the sternum. Paroxysms of coughing may be excited by changes in outside temperature.

Such a cough is a reflex set up by irritation to the mucous membranes of the larynx, trachea or bronchi. After secretions have become copious and liquid, the cough will not be so distressing but may be more frequent.

Case 12. Female, age 50, consulted me May 15, 1923 for a dry, ringing cough of six months duration. She had previously consulted four other physicians without benefit. I made cutaneous tests; by avoiding those foods to which she was sensitive, she was completely relieved within two weeks.

Case 13. Female, age 12, was brought to me on July 10, 1924, for petit mal attacks of six months' duration. An allergen-free diet completely relieved the seizures.

Four months later this patient developed a constant, sharp, ringing cough which the mother believed might be pertussis. On examination, I found that the entire left lung gave harsh, rough sounds. Further examination, elicited a tentative diagnosis of abscessed left second lower biscuspid tooth, which was confirmed by X-ray examination. Twenty-four hours after the offending tooth had been extracted, there was a fifty per cent reduction in the cough; in three days, it was completely relieved.

Here we have an example of absorption of bacteria and bacterial toxins, directly affecting an entire lung. It is also interesting to note that even with so severe an infection, there was no recurrence of the epileptic seizures.

Case 14. Female, age 22, telephone company employee, came to me after having been referred by the company physician to a nose and throat specialist in the hope of determining the cause of a cough of three month's duration. This specialist, unable to find anything definite, sent her on to the nose and throat department of the Massachusetts General Hospital, where she was used as a demonstration subject for a class of students, still without eliciting a definite cause for the cough.

It was at this point that she came to me. Upon examination, I found an infected tonsil, which proved to be the cause of the cough.

Case 15. Female, age 53, was referred to me by her family physician, for hypertension. She had had a systolic pressure of 190 for at least fifteen years. Her history included headaches, arthritis, and a cough which was extremely severe in the morning and recurred frequently thoughout the day. She had had hypertension for twenty years that she knew of, accompanied by dizziness and tinnitis in both ears. Her systolic pressure was 200. The family physician had advised that she have her uvula "clipped," to relieve the cough.

At the time of consultation, the patient was taking a vitamin preparation, which I requested stopped during the test period. Within forty-eight hours, the cough was much reduced. Following cutaneous tests and the adoption of an allergen-free diet, the cough was completely relieved, also the headaches, dizziness, tinnitus and arthritis. Two weeks after instituting the diet, her systolic pressure had fallen to 150.

In cases 12, 14, and 15, examination of the lungs elicited no physical findings, while in case 13 the cough was associated with definte rough, harsh breathing sounds throughout an entire lung. In case 15, although there was some edema and elongation of the uvula, which might justly have been blamed for the cough, partial relief was obtained simply by the omission of the vitamin preparation which the patient had been taking followed by complete relief as soon as allergenic foods were omitted.

Cough is the most noticeable symptom in bronchitis; it is never absent. In this condition, it may be slight, or again exteremely severe and of a loud, ringing character. The sequence already mentioned, first dry, later productive, appears here also. These changes may be either vasomotor or inflammatory in origin, or a combination of both.

BRONCHITIS

Bronchitis is usually described as a catarrhal condition of the bronchial tubes; however, the same might be said of any other form of inflammation. Frequently all layers of the bronchial wall are involved. It may occur in persons of any age.

For clinical purposes, it is necessary to distinguish between the acute and the chronic forms of this condition. Into which classification a given case should fall, depends as much upon the condition of the bronchial mucous membrane and upon the patient's general health as upon the duration of the disease or the actions of the etiologic agent. The same cause, therefore, may, in one instance excite an acute, and in another, a chronic attack of bronchitis.

Many pathogenic microörganisms are normally present at all times in the upper air passages, in the trachea and the larger bronchi. Before any of these therefore, can excite an inflammatory condition, it is necessary either that their activity be increased or that the resistance of the mucous membrane be diminished. In some cases, they acquire this greater virulence in some other part of the body, as for example, in case 15 above. Here a cough and rough breathing associated with an inflammatory condition in the lung, followed the development of an abscess in a tooth. When the original seat of infection was removed by the extraction of the tooth, the inflammation in the respiratory tract also quieted down. In case 14, we saw the same thing happen following development of a tonsillar abscess.

In the second case, that in which the natural resistance of the mucous membrane has been reduced, we find a variety of causitive factors. Such changes may range all the way from very slight to extremely marked.

Case 16. Male, aged 35, consulted me on April 22, 1929, then said there was nothing wrong with him! In the course of a careful history-taking, I asked him if any mucus ever came up into his throat, to which he replied in the affirmative.. His systolic blood pressure was 110, diastolic 60. I made cutaneous tests and prescribed a suitable diet. In two weeks he reported that he no longer had mucus coming up into his throat and that he was also relieved of a "full feeling" in the abdomen. He then said he had always had this "full, tight feeling" but believed it natural. At this time his systolic blood pressure was 120, diastolic 70.

This case resembles case 11 in some respects. In that case, elimination of allergenic foods gave a singer greater endurance and strength of voice; in case 16, the small daily production of mucus was the noticeable symptom. In both cases, a mild form of bronchitis proved to be entirely of allergenic origin.

Sometimes the causative inflammation may not be at the site to which soreness is referred by the patient. I myself, on one occasion, felt soreness in the larynx, but the laryngoscope revealed no inflammation. Forty-eight hours later bronchoscopic examination revealed marked congestion at the bifurcation of the bronchi.

In those cases of cough where mucus is slight or absent, the amount of vasomotor disturbance is also slight. As greater sensitivity to allergenic foods or inhalants develops, greater hyperemia of the tracheal and bronchial mucosa, with increased vasoparesis and increased secretion of mucus will develop. With suitable conditions of temperature and humidity, conditions also favorable to the growth and increasing virulence of microörganisms throughout the respiratory tract, the absorption of bacterial toxins and debris adds to the toxic allergy. The severity of the results depends upon the allergic and bacterial sensitivity of the individual. Other factors which may aggravate the condition are cold, dampness, fatigue, loss of sleep, inhalation of irritating vapors, powders, pollens or tobacco, and many others. Chilling of the body surface, or portions thereof, by cold winds or an electric fan, contact with cold, damp air, standing on a very cold surface until the body is chilled, all these are examples of the combination of high humidity and draft or chilling which may make trouble. Perspiring freely after exertion of itself may do no harm; the harm will come from allowing such perspiration to cool, leaving clammy skin and damp, cold clothing. These in turn produce contracture of the surface veins, followed by dilatation or paresis of the respiratory vascular system. Other bodily systems can also be affected by this sudden change from warm to cold-and-damp.

ASTHMA

In some asthmatics, the typical symptoms may be preceded by sneezing, vasomotor rhinitis or other upper respiratory affections, such as have already been outlined in this paper. Or they may occur only after the onset of the asthmatic attack. Or again, a marked watery nasal discharge may appear as the bronchitis and asthma begin to subside.

Persons with asthma or other manifestations of respiratory allergy, also have a predisposition to other disease conditions. Or possibly it would be more correct to say that the underlying condition which excites the disease, whether hereditary or acquired, is also the chiefly important cause of the asthma.

Hereditary predisposition sometimes displays itself as a direct transmission of allergic tendency from parent to child; in other cases, the parent of an asthmatic child may not have asthma but may show evidence of some other form of allergenic disturbance. I have pointed out elsewhere, also, that many of these vasomotor respiratory disturbances may be associated with gastrointestinal affections, dermatitis, arthritis or normal, subnormal or vascular hypertension; the patient may also be tired, weak or exhausted. Asthmatic patients, in addition, are extremely sensitive to cold, dampness or sudden changes in temperature.

Case 17. Male, age six, was brought in consultation on May 4, 1945. He had had asthma for two years. His nose was "stuffy" most of the time with a thick, white nasal discharge. He ran a temperature with the asthmatic attacks, of which he had had four in the preceding three months. The last had been two weeks previously. Between attacks, he coughed frequently and complained of headaches. At six months of age, he had had eczema. He sometimes complained of pain in the lower right quadrant of the abdomen. He urinated very frequently and wet his bed. At night, he perspired so profusely that pillow and pajamas had to be changed.

Family history showed that the father and grandfather had had asthma, the maternal grandmother had arthritis, the paternal grandmother had asthma. With such an inheritance, is it any wonder that this child should have asthma and vasomotor rhinitis?

Elimination of allergenic foods, identified by cutaneous tests, brought complete relief from asthma, sneezing and nasal discharge, also stopped the frequency, bed-wetting and excessive sweating. To date (May, 1948), there has been no recurrence. It is interesting to note that this

child had previously been tested by another allergist without results.

Case 18. Male, age five, brought for consultation September 4, 1947. He had had asthma for three years. At first the attacks had lasted three or four days once a month, these attacks being accompanied by fever. With the advent of cold weather, the attacks had increased in frequency to about one a week; in one of these, oxygen was used. "Stuffiness" of the nose, and severe coughing spells with mucus coming into the throat, especially at night, also in the early morning, had appeared in the last six months. He had had rheumatic fever one year previously. The last two weeks, he had complained of pains in his legs; when running he "lopped over sideways." It was noted that he did not have the amount of energy normal to children of his age. There was extreme frequency of urination; the amount was large, so that when urgency overtook him, he often could not reach the bathroom in time to avoid an accident. He wet his bed also; in addition, perspiration at night was so profuse that his nightclothes and pillows had to be changed.

Physical examination revealed a systolic heart murmur at the apex. There were many rales and harsh, rough breath sounds in the lungs. Abdominal distention, with gas, was marked. Both knees and ankles showed evidence of arthritis.

Elimination of allergenic foods brought about complete relief of all symptoms, asthma, cough, fever, sweating, urgency and incontinence, pains in legs and lack of energy. He was then able to run and play like other children his age. This patient, like that in case 17, also had previously been tested by another allergist, without obtaining relief.

Case 19. Female, age 50, consulted me on September 20, 1940, for continuous asthma of 20 years' duration. So severe was her condition that she carried an inhaler with her at all times, even in going from one room to another in her own home. On entering my office, she had to make use of it before she could speak to me. A diet based on the results of cutaneous tests relieved her condition completely, as evidenced when she returned for check-up on October 7. She remained in good health for six months; then, being one who preferred good eating to good health, apparently, she had a severe recurrence of the asthma, together with continuous and marked gastro-intestinal distress as well.

Case 20. Female, aged 53, consulted me on September 10, 1928, complaining of asthma of 33 years' duration. There were frequent increases in the severity of the attacks. Simple dietary restrictions, following cutaneous tests, brought fifty per cent improvement in two weeks' time, with complete relief in four weeks. The patient also seemed much stronger.

The patients cited in both of the preceding two cases, like several others in this series, had previously consulted other allergists without obtaining any relief.

Case 21. Female, age 19, was brought to me by her mother on September 10, 1928, who stated frankly that she did not expect me to be able to do anything for her daughter's asthma, as many other physicians had already tried and failed. The attacks had recurred for the past six years, often with such severity that the patient was forced to remain in bed for six months at a time. At these times her breathing was so labored that she could be heard all over the house. At one time, the administration of adrenalin had nearly killed her.

I prescribed a diet following cutaneous tests. One week later, the mother telephoned to say that the patient was in bed again. The day after she had begun to follow the prescribed regime, she had complained all day of feeling chilly. The next day she began having slight asthma; the mother, expecting another of her severe attacks, called the family physician, who commented on her changed condition and prescribed some medicine. The mother commented to me that the present attack was different and much lighter than the previous ones. I ordered all medicine stopped and instructed that she report to me in forty-eight hours. When the report came in, it showed complete recovery both from the immediate symptoms and from the asthma.

Here we have a case where the patient had taken a cold within twenty-four hours of starting her allergen-free diet and before all of her allergens had been eliminated from her system. This had brought on the asthma attack. That she persisted in her treatment accounts for the mildness of the attack and her prompt recovery.

This patient also proved to be sensitive to a number of pollens prevalent between April and October. She was successfully treated for these also. This demonstrates the value of eliminating allergenic foods and giving pollen injections simultaneously.

Case 22. Female, age 19, consulted me on May 5, 1931, for asthma of seven years' duration. The week prior to this consultation, she had had so severe an attack that — her mother stated — she had "gone black." The family physician, being at a loss for further treatment had sent her to me. The patient appeared weak, exhausted, without interest in her surroundings. Just two weeks on an allergen-free diet found her cured of her asthma and with energy enough to take a normal interest in life.

Case 23. Male, age 22, a native of New Brunswick, Canada, consulted me on March 10, 1923, for asthma. This patient was attending school in Boston. The previous Christmas, while on vacation at home, he had been taken in the night with asthma so severe as to keep him in bed until the day before he appeared at my office. On the train coming down, he had found his asthma growing less severe. When I first saw him, he was pale, emaciated and looked exhausted; he gave a fair picture of being in the last stages of tuberculosis. Cutaneous tests revealed certain foods to which he was allergic; also horse "dander" showed up as an allergen. Questioning him, I found that there was a horse stable an eighth mile from his home on the same side of the house as his bedroom. Although the weather had been extremely cold, so that no windows had been open on that side, the sudden onset of the asthma on the very night of his return home, suggested that the occupants of the stable had provided the final exciting factor in a patient who was already allergic to some foods. It seemed that the combination of those foods, with the inhalation of the horse "dander" was what had kept him in bed so long. My conclusion was further borne out by the evidence of his improvement as soon as he left home. I advised him not to go home again, but to return to school, which he did. In two weeks, he was free not only of his asthma but of its attendant cough as well. He continued so thereafter. For a number of years, each fall I received messages from returning hunting parties, who said that the lad's parents wanted me to know how well he had remained to that time.

Case 24. (Allergy as a factor in unresolved pneumonia) Male, age 52, originally consulted me on May 5, 1922, and at intervals of nine, three and two years thereafter, for cough, asthma and eczema, all of which were completely relieved by the elimination of allergenic foods.

The present consultation was on February 10, 1937. The previous December, this patient had had a severe pneumonia and had been under an oxygen tent. Following this illness his cough and asthma had recurred. Examination

showed dullness in the lower left lobe of the lung with no air entering this consolidated area. Cutaneous tests were again made and a suitable diet prescribed. One week later, the patient reported that he had begun to cough up a dark greyish substance, round in form and two or three inches long. "They looked like worms." After five days of this both cough and asthma were seventy-five per cent relieved.

On March 2, I examined this patient again. At this time all dullness of the lobe had completely disappeared, also the asthma, cough and sputum.

Case 25. Female, age 57, was referred by the patient cited in the previous case on June 23, 1943. Her complaints were of cough, sneezing, watery nasal discharge, "raising" yellow or greenish sputum which also varied in consistency, a "raw feeling" beneath the sternum, frequent and severe headache which might be either dull or sharp, a feeling as of "steam letting off" in both ears, fissures in the nares, sore eyes "like something was in them all the time," itching of the face which was aggravated by hot water, washing or friction, frequent colds and sore throat during the preceding winter, pains in chest, shoulders, lumbar region, knees and ankles which were worse in damp or cold weather, excessive perspiration most of the time, especially when walking, and finally "very tired in the moning." She had had a cough for the past twenty years, which recurred in spells every five or ten minutes throughout the day. She had had pneumonia the preceeding April, which was followed by an increase in the severity of all her other symptoms.

Physical examination showed dullness over the lower left lobe of the lung, with no air entering the area. Cutaneous tests were made and a diet prescribed. On July 10, she reported that the cough had lessened after one week on the diet. On July 17, the sputum had changed from green to a light yellow and she reported that much more mucus was raised without much coughing. Over the lower left lobe, harsh, rough breath sounds were audible. On August 11, a letter from this patient stated that, as a result of the diet, there was a definite improvement in her condition, that she now coughed very little with only a slight amount of thin mucus. In October, she reported that the cough and mucus had disappeared and that she was feeling well.

In this patient also we have a picture of a long list of allergenic disturbances extending over a protracted period of time, and recently complicated and aggravated by an unresolved pneumonia. All of the older symptoms were abated and the pneumonic condition cleared up simply by eliminating from her diet those foods to which she was sensitive.

CONCLUSIONS

1. Allergy may occur in any or all areas of the respiratory tract from the nares to and including the lungs.

2. Such allergic disturbances may occur in patients of any age.

3. Individual areas in the respiratory tract may be affected by allergenic disurbances at the same time that other systems of the body are similarly affected.

4. Pharyngeal and nasopharyngeal conditions are especially likely so to occur.

5. There is evidence that hereditary predisposition plays a definite part in such disturbances.

6. Such hereditary predisposition does not necessarily appear as familial occurrence of the same condition; merely the tendency to *some* sort of allergenic disturbance seems to be what is inheritable.

7. In some allergy patients, adrenalin may cause serious illness.

8. Elimination of irritating inhalants and of allergenic foods from the diet, together with removal of any foci of infection, will relieve the symptoms of suffering from respiratory allergies.

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NUTRITION

Gastro-Intestinal Food Hypersensitivity: Roentgenographic Demonstration

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THE LITERATURE IS REPLETE with clinical observations suggesting that the small bowel is intimately involved in the production of symptoms caused by the ingestion of certain foods in food-hypersensitive persons.

However, there appear to be few records (1, 2, 3, 4) of controlled, systematic study of small intestinal behavior in groups of patients hypersensitive to certain foods. For this reason, we have attempted by the following study: (a) to determine if specific hypersensitivity to foods results in any consistent roentgenographic changes in the small intestine; (b) to determine if similar changes occur in persons not manifesting food hypersensitivity and (c) to devise a roentgenographic procedure to study the behavior of the food-hypersensitive intestine.

HISTORICAL

The earliest inferences that certain foods may cause disturbances in otherwise normal persons are found in pre-biblical and biblical literature. Hippocrates (5) stated unequivocally, "Do not give milk to people with headaches." Lucretius (6) (First Century B. C.) is credited with coining the phrase "One man's meat is another man's poison." Galen (7) (130-200 A. D.) was aware of such a thing as sensitivity to goat's milk. The Babylonian Talmud (8) (Second Century) gives precise instructions as to how to combat intestinal hyper-sensitivity to eggs by using an appropriate egg albumin preparation.

Spigelius and Riolan (9) (1645) reported an autopsy performed immediately after the death of a man following the ingestion of a heavy meal. The important finding was massive spastic contraction of the small and large bowel. Willis (10) (1685) reported asthmatic paroxysms after the ingestion of certain foods. Howship (11) (1830) described colonic spasms in patients manifesting food sensitivity.

The earliest description of roentgenographically demonstrated changes in the gastro-intestinal pattern was reported by Holzknecht (12) who, in 1906, observed antral spasm, hyperperistalsis and gastric retention after the administration of certain foods mixed with bismuth and water.

Osler (13) (1914), Crispin (14) (1915) and Christian (15) (1917) all described acute visceral manifestations due to food sensitivity and suggested angioneurotic edema as the possible cause. This assumption was based on the finding of abnormalities in the roentgenographic examination of the gastro-intestinal tract of their patients and on laparotomy findings of Mayo (16), Riggs (17) and Morris (18) who observed edema of the stomach, ileum and colon without organic lesions demonstrable by gross or histologic methods.

Wiedemann (19) (1921) and E. Urbach (20) (1923) described in detail roentgenographic changes in the motility and pattern of the stomach in food-sensitive patients. Their main findings consisted of: (1) tonic spasm of the antrum with almost complete obstruction; (2) hypermotility of the body and fundus; (3) gastric retention and (4) hypersecretion.

Eyermann (21) and Vaughan (22) noted hypertonicity of the transverse and descending colon when the specific food was mixed with the barium in food sensitive patients.

Serio (3) studied the effects of food in sensitive and non-sensitive patients and found spasm of the stomach and intestine, hypomotility of the stomach and antiperistalsis in sensitive patients, while the controls showed no abnormalities of pattern or motility. Rowe (23) and Andresen (24) demonstrated spasm, hy-

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per-motility, coarsening of mucosal folds, rapid and reverse peristalsis occurring in the small intestine resulting from food hypersensitivity. Fries and associates (4) studied the radiographic changes in the gastro-intestinal tract of thirty food-sensitive children. They reported gastric retention, increased or decreased gastric motility, occasional small intestinal hypermotility, some segmentation and scattering of the barium in the small intestine and spasm or dilatation of the colon. Golden (25) felt that the changes in the small bowel which he found in a patient sensitive to milk were comparable to the typical abnormalities occurring in certain "deficiency states." Wing and Smith (1) studied the small bowel pattern in nine cases of suspected food hypersensitivity but were able to demonstrate significant changes only in three. Their experimental studies of the small bowel of parenterally sensitized guinea pigs gave negative results. Several reports (26) have been made of isolated cases of food sensitivity with various roentgenographic abnormalities of the pattern and motility of the small intestine.

METHODS AND MATERIAL

From the material scattered throughout the literature, it appears that abnormalities of the small bowel may be associated with food sensitivity. There is, however, a wide divergence in the description of the changes. Since the abnormalities cited are not specific for food sensitivity but also occur in deficiency diseases (27), hypoproteinemia (28), nephrosis (28b), diabetes insipidus (28b), acute gastro-enteritis (28, 29) and hyperthyroidism (30), it was felt necessary to study the problem under carefully controlled conditions.

Three groups of patients were investigated:

Group A consisted of 12 patients with a history and clinical symptoms of food hypersensitivity of the gastro-intestinal tract.

Group B comprised eight non-allergic persons. This group was studied to determine if the foods tested in group A could produce small bowel abnormalities in non-sensitive persons.

Group C contained five patients with cutaneous or asthmatic manifestations of food hypersensitivity but without clinical evidence of gastro-intestinal disturbances. These patients were investigated to study the occurrence of abnormalities of the small bowel in subjects who react allergically in tissues other than those of the gastro-intestinal tract.

Identical procedures were used in all three groups. A study of the small bowel with barium sulfate and water was performed and followed four to five days later by an identical roentgen series using barium, water and the suspected allergen. This afforded opportunity for comparison of the pattern and motility of the small bowel in the presence and in the absence of the suspected allergen. Of all the studies reported, only those of Wing and Smith (1) (nine adults), Golden (2) ("several" adults), Fries and associates (4) (30 children) and Cooke (26c) (one adult) were made in this manner.

TECHNIC

All patients were instructed to eliminate completely the food to be tested from their diet for at least five days before receiving the preparation of barium and water. No food or liquid was permitted after midnight before the day of the study and breakfast was omitted. On the morning of the examination, the patient was given 240 cc. of the opaque mixture, consisting of 120 cc. of chemically pure barium sulfate (Mallinckrodt-USP XII) in an equal amount of tap water. Roentgenograms of the abdomen were taken after 1, 2, 3, and 6 hours, with the patient in the supine position, using par-speed double intensifying screen, Potter-Bucky diaphragm and a rotating anode tube. The stomach and duodenum were not studied fluoroscopically as all patients had had previous studies of the upper gastro-intestinal tract without showing abnormalities.

Five or more days later, the examination was repeated under identical circumstances, except that the food to be studied was added to the opaque medium. This was done either by suspending 120 cc. of the barium sulfate in an equal quantity of the liquid food or by adding 60 Gms. of the finely ground solid food and sufficient water to make a total of 240 cc. As far as possible, patients were kept unaware of the admixture of food to the contrast medium. No food or liquid was given during either study.

In each case, the roentgenograms of both the barium-water and barium-allergen studies were compared simultaneously, using an 8-section view box, in order to evaluate readily the comparative changes between the two series.

RESULTS

Before the roentgen findings can be discussed, certain terms used in the description of the abnormalities must be defined:

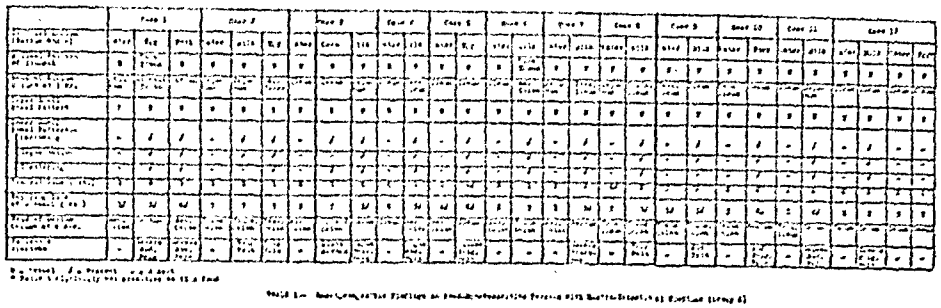
1. Narrowing: Multiple areas of varying length of narrowing (below 1.5 cm.) in the caliber of the small bowel.

2. Segmentation: Loss of continuity of the barium column due to breaking up into small boluses, separated by areas of narrowing.

3. Scattering: Quantities of barium of varying size retained in the ileum after the tail of the barium column has passed.

4. Transit Time: Time after swallowing required for the barium to reach the cecum.

Group A. (Twelve patients with gastro-intestinal food hypersensitivity). The mucosal pattern of the stomach was normal in all of the barium-water examinations but the folds appeared wide and edematous in two of the barium-allergen series (cases 1 and 6). In the barium-water studies, none of the opaque



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medium reached the cecum in one hour, while it did so in six instances with the barium-allergen mixture (cases 1, 2, 3, 6 and 10). (Some of the cases had more than one allergenic study when sensitivity to more than one allergen was suspected). In all studies, the pattern of the upper part of the small bowel was normal.

The most striking changes in this group were in the lower half of the small bowel. Numerous areas of narrowing were noted in all of the barium-allergen studies. Segmentation occurred in all but one (case 3). Scattering was present in all but two of the barium-allergen examinations (cases 2 and 9). None of these abnormalities were seen in the corresponding barium-water series.

The emptying time of the stomach, using barium and water, ranged from one to six hours, with the stomach empty at six hours in all the examinations. There was retention after six hours in four of the barium-allergen series (cases 1, 5, 10 and 11).

None of the patients were discomforted by the barium-water studies, while all but one (case 6) complained of severe distress during or shortly after receiving the barium-allergen mixture. The symptoms varied from epigastric distress and nausea to severe abdominal pain and diarrhea, which were the duplication of the clinical complaints of the patients. One patient (case 3), in addition to having gastro-intestinal manifestations, had an asthmatic attack.

One patient (case 12) had certain additional studies performed. A second barium-water study was made five days after the abnormal barium-allergen (milk) series and was normal again. This patient was also tested by using a food (egg) to which he was not clinically hypersensitive. This study was normal, making it appear that the described changes in the small bowel do not occur when a food sensitive patient ingests food to which he is not specifically hypersensitive.

The information gathered from the study of group A is listed in Table I.

The following two histories are representative of group A.

Case 1. I. H., a 35-year-old white woman was admitted to the Medical Ward on 7 May, 1947 complaining of nausea, vomiting and headache following the ingestion of certain foods. She had been extremely sensitive to egg and pork since early childhood. As long as she can remember, her symptoms began with uneasiness one to two hours after the ingestion of the offending food with pain, nausea and vomiting following and becoming more severe 12 to 36 hours later. On admission, the patient had been vomiting almost constantly for two weeks and had lost 9.1 Kg. (20 lbs. during this time.

Her mother suffered from migraine, aggravated by milk and the patient had cylic vomiting and diarrhea in childhood, aggravated by egg and pork. There were occasional migraine-like headaches since the menarche at age 13 and frequent aphthae, coating of the tongue and flatulence.

At the time of admission, the patient was a fairly well-developed and well-nourished but severely dehydrated white woman without other abnormal findings on physical examination except for slight generalized abdominal tenderness. Skin tests for egg and pork were negative.

Small Bowel Studies: The barium-water study showed nothing abnormal. In the barium-egg test, the mucosa of the stomach was edematous and showed widening of the rugal folds. At one hour, the head of the barium column was in the sigmoid colon and at six hours, in the rectum. The pattern of the upper small bowel was normal but there was narrowing, segmentation and scattering of the barium in the ileum. The stomach was empty at the end of three hours. The transit time was two hours. In the barium-pork test, the mucosal pattern of the stomach was normal. At one hour, the head of the barium column was in the cecum; at six hours, in the ascending colon. The upper small bowel pattern was normal but there was narrowing, segmentation and scattering of the barium in the ileum. There was gastric retention at the end of six hours. The transit time was one hour. During both the barium-egg and barium-pork studies, the patient developed severe abdominal cramps.

The roentgenographic findings are shown in Fig. 1 and tabulated in Table I.

Case 2. T. K., a 42-year old white male, machine operator, was admitted to the Medical Out-Patient Department on 14 March, 1947, complaining of abdominal distress for four years. Soon after the onset of World War II, while under the physical and mental stress of war work, the patient noticed the onset of vomiting shortly after his usual breakfast which consisted of bacon and eggs. He soon discovered that the vomiting could be prevented by the elimination of the eggs. However, a sense of epigastric fullness, abdominal distress, distention and loose stools were present almost constantly, even after the elimination of the eggs. The ingestion of milk appeared to increase these symptoms. The patient had lost 6.8 Kg. (15 lbs.) in one year.

There was no family history of allergic diseases. The patient was strongly sensitive to rhus toxicodendron. His dietary habits were average. He was a well-developed,

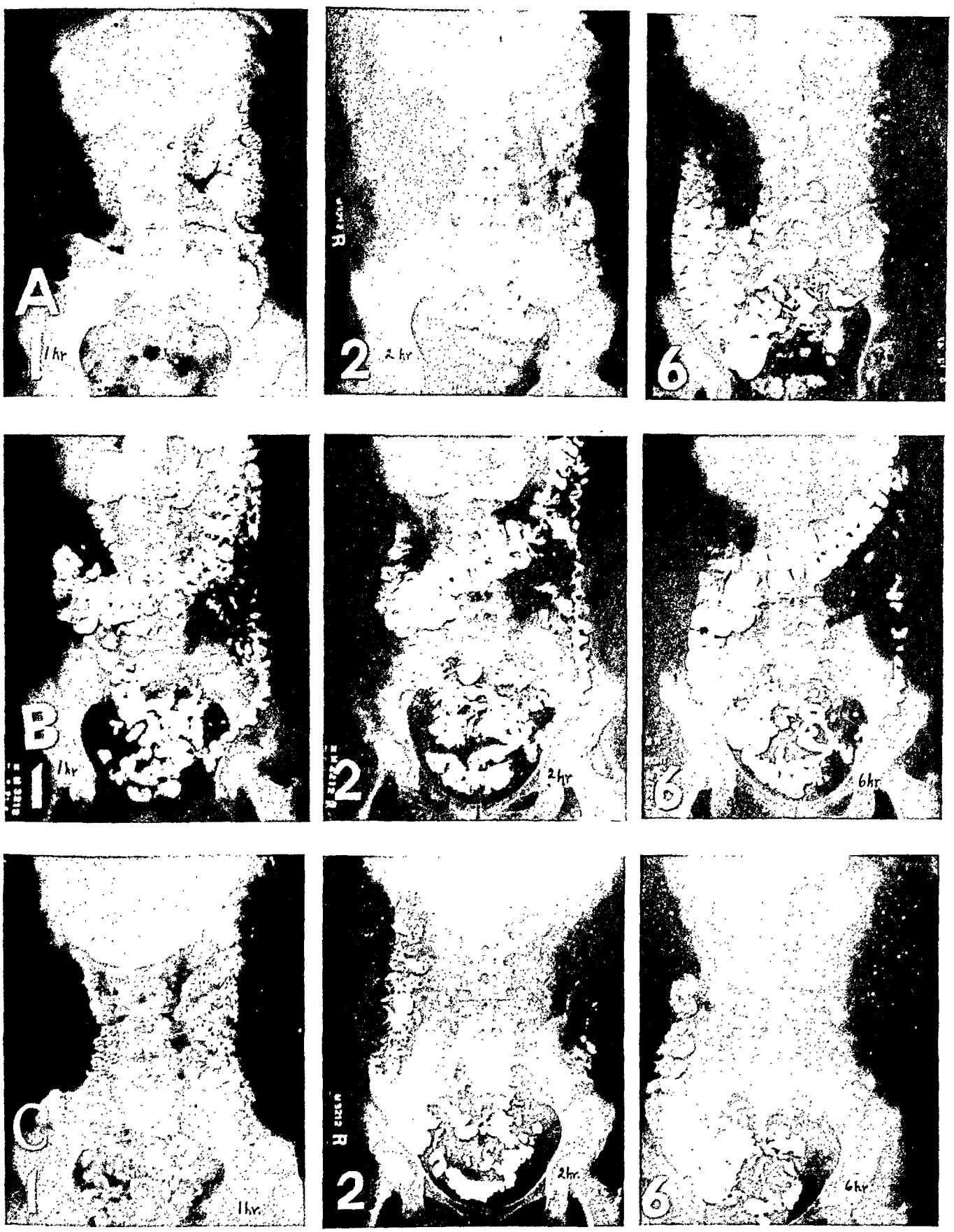


Fig. 1. — (Case 1). Roentgenograms taken at 1, 2 and 6 hours of a patient with ga stro-intestinal hypersensitivity to egg and pork.

Row A. — Barium-water study showing no abnormalities.

Row B. — Barium-water-egg study showing hypermotility with narrowing segmentation and scattering in the ileum.

Row C. — Barium-water-pork study showing hypermotility, narrowing, segmentation and scattering in the ileum and 6 hour gastric retention.



Fig. 2. — (Case 2). Roentgenograms taken at 1, 2 and 6 hours of a patient with gastro-intestinal hypersensitivity to milk and egg

Row A. — Barium-water study showing no abnormalities.

Row B. — Barium-water-milk study showing hypermotility with narrowing and segmentation in the ileum.

Row C. — Barium-water-egg study showing hypermotility with narrowing, segmentation and scattering in the ileum.

	Case 13		Case 14		Case 15		Case 16		Case 17		Case 18		Case 19		Case 20	
Diagnosis	Inguinal Hernia		Inguinal Hernia		Rheumatoid Arthritis		Inguinal Hernia		Simple Mastectomy		Inguinal Hernia		Simple Mastectomy		Inguinal Hernia	
Contrast media (Barium sulf.)	Water	Milk	Water	Milk	Water	Egg	Water	Egg	Water	Pork	Water	Pork	Water	Corn	Water	Corn
Mucosal pattern of stomach	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Head of Barium Column at 1 Hr.	Jejunum	Jejunum	Ileum	Ileum	Ileum	Ileum	Ileum	Ileum	Jejunum	Ileum	Jejunum	Ileum	Cecum	Cecum	Ileum	Jejunum
Upper small Bowel Pattern	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lower Small Bowel Pattern:- Narrowing	-	-	-	-	-	-	✓	✓	-	-	-	-	✓	✓	-	-
Segmentation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Scattering	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-
Transit Time (hrs.)	3	3	3	3	3	3	2	3	3	3	2	2	1	1	2	3
Emptying Time of Stomach (hrs.)	3	3	3	3	3	3	3	3	3	3	3	2	2	2	3	3
Head of Barium Column at 6 Hrs.	Ileum	Cecum	Asc. Colon	Asc. Colon	Cecum	Cecum	Cecum	Cecum	Ileum	Asc. Colon	Desc. Colon	Trans. Colon	Asc. Colon	Asc. Colon	Rectum	Trans. Colon
Patient's Symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

N = Normal ✓ = Present - = Absent

TABLE I.— Roentgenographic Findings in Non-Sensitive Persons (Group B)

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well-nourished adult in no immediate distress. Physical examination showed no abnormalities. There was no abdominal tenderness. Skin tests for milk and egg were negative.

Small Bowel Studies: The barium-water study was normal. In the barium-milk test, the mucosal pattern of the stomach was normal. At one hour, the head of the barium column was in the jejunum; at six hours, in the transverse colon. The upper small bowel pattern was normal. There was narrowing and segmentation of the barium in the ileum. The stomach was empty at the end of three hours. The transit time was two hours. In the barium-egg study, the mucosal pattern of the stomach was normal. At one hour, the head of the barium column was in the ascending colon; at six hours, in the descending colon. The upper small bowel pattern was normal but there was narrowing, segmentation and scattering of the barium in the ileum. The stomach was empty at the end of three hours. The transit was one hour. During both the barium-milk and barium-egg examinations, the patient had nausea and epigastric distress.

The roentgenographic findings are shown in Fig. 2 and tabulated in Table I.

Group B. (Eight patients not manifesting food hypersensitivity). The effects of milk, egg, pork and corn on this group were determined by using two persons for the study of each food. In all patients in this group, the mucosal pattern of the stomach was normal in both the barium-water and barium-food studies. In one patient (case 19), the barium reached the cecum in one hour but this occurred in both examinations and was not considered significant. The upper small bowel pattern was normal in all studies. The pattern in the lower portion of the small bowel showed narrowing of the lumen in two cases (cases 16 and 19) but this was present both with and without the food. There was no evidence of segmentation in any of the studies. Scattering occurred in cases 13 and 16 in the barium-water study only. The transit time varied from one to six hours, and, in all but case 17, the transit times with and without the allergen paralleled each other. The emptying time of the stomach was two to three hours, except in two cases (cases 16 and 17) where a small three hour residue had disappeared at six hours. None of the eight patients had any untoward symptoms during these studies.

The information gathered from the study of group B is listed in Table II.

The roentgenographic findings of a representative case of this group (case 15) are shown in Fig. 3 and summarized in Table II. This patient had chronic rheumatoid arthritis and was hospitalized for roentgen therapy to the lumbo-sacral area. It will be seen that the barium-water and barium-food (egg) series were similar.

Group C. (Five food hypersensitive patients without gastrointestinal disturbances). One patient in this group (case 21) suffered from bronchial asthma, induced by the ingestion of milk; a second (case 22) from angioneurotic edema, induced by eating peas; the remaining three had neurodermatitis, which was aggravated in two (cases 23 and 25) by chocolate and in the other (case 24) by milk.

No unusual changes were seen in the mucosal pattern of the stomach and upper small bowel in any case with either barium-water or the barium-allergen mixture. The pattern in the lower part of the small bowel showed no segmentation or scattering in any study. In one instance (case 24) narrowing was present after the barium-water study but absent when the allergen was added. In case 22, narrowing occurred in both studies. The transit time varied from one to three hours, except in case 25 where it was six hours with barium-water and three hours with barium-allergen. Emptying time of the stomach varied from two to six hours. There was no exacerbation of the symptoms of any of the patients during or after the barium-water studies but allergic manifestations developed or increased in all cases within 24 to 36 hours after the ingestion of the allergen.

The information gathered from the study of group C is listed in Table III.

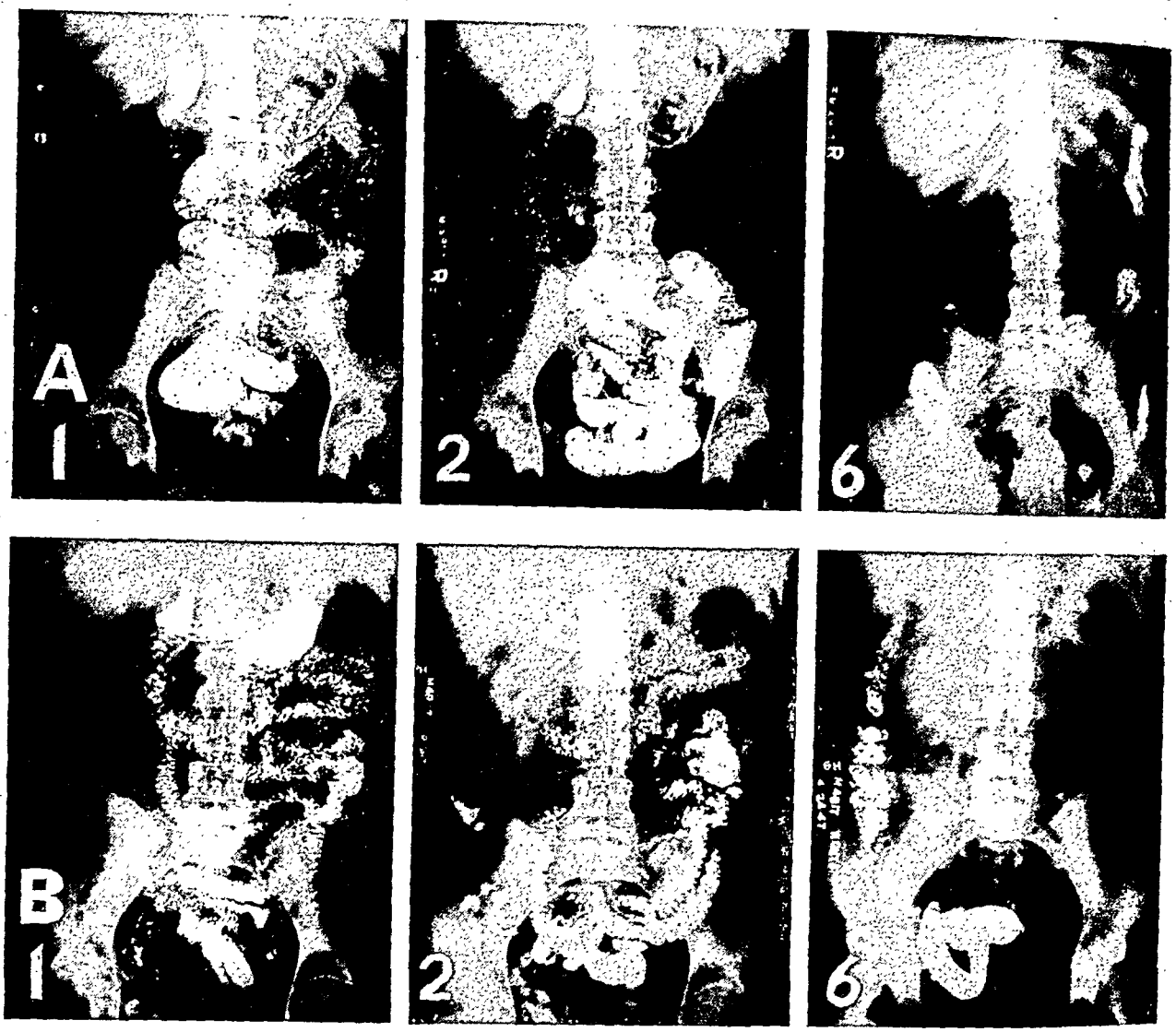


Fig. 3. — (Case 14). Roentgenograms taken at 1, 2 and 6 hours of a non-sensitive person, using egg in the contrast medium.
Row A. — Barium-water study showing no abnormalities.
Row B. — Barium-water-egg study showing no abnormalities.

	Case 21		Case 22		Case 23		Case 24		Case 25	
Diagnosis	Bronchial Asthma		Angioneurotic Edema		Neuro-dermatitis		Neuro-dermatitis		Neuro-dermatitis	
Contrast medium (Barium mix:-)	Water	Milk	Water	Pork	Water	Chocolate	Water	Milk	Water	Chocolate
Duodenal Pattern of Stomach	N	N	N	N	N	N	N	N	N	N
Level of Barium Colunc at 1 Hr.	Ileum	Cecum	Ileum	Ileum	Ileum	Ileum	Trans. Colon	Trans. Colon	Hepat. Flex	Ileum
Upper Small Bowel Pattern	N	N	N	N	N	N	N	N	N	N
Lower Small Bowel Pattern-Narrowing	-	-	+	+	-	-	+	-	-	-
Intussusception	-	-	-	-	-	-	-	-	-	-
Clustering	-	-	-	-	-	-	-	-	-	-
Ileocecal Valve (Area.)	3	2	2	2	2	3	1	1	3	3
Evacuation Time of Stomach (Hrs.)	2	3	3	3/	2	2/	2	3/	3	3
Level of Barium Colunn at 6 Hrs.	Asc. Colon	Trans. Colon	Asc. Colon	Asc. Colon	Asc. Colon	Asc. Colon	Trans. Colon	Trans. Colon	Cecum	Asc. Colon
Patient's Symptoms	-	Asthmatic Attack	-	Angioneurotic Edema Urticaria	-	Exacerbation of Neuro-dermatitis	-	Exacerbation of Neuro-dermatitis	-	Exacerbation of Neuro-dermatitis

N = Normal + = Present - = Absent

Table 5.- Roentgenographic Findings in Food-Hypersensitive Persons with Symptoms other than Gastro-Intestinal (Group C)

Use magnifying glass if necessary

The following history is representative of group C.

Case 21. M. R., a 52-year-old white woman was admitted to the Medical Ward on 29 July, 1947 with the complaint of bronchial asthma for 32 years.

After the birth of her child, in 1914, and a subsequent severe upper respiratory tract infection, she developed seasonal bronchial asthma, present from April to September. Skin tests with house dust and certain pollens were strongly positive. The asthmatic attacks were never severe until two years before admission, when the patient became greatly disturbed by family difficulties. Since then, any nervous upset has provoked asthmatic symptoms. For the past 10 years she has noted that small amounts of milk and moderate quantities of egg and pork elicited immediate asthmatic seizures. The patient had exudative dermatitis in childhood; two aunts had asthma and migraine.

She was a well-developed and well-nourished woman in no immediate distress. The only important abnormal physical findings were bilateral emphysema and many musical rales in both lungs. Skin tests for milk, egg and pork were negative.

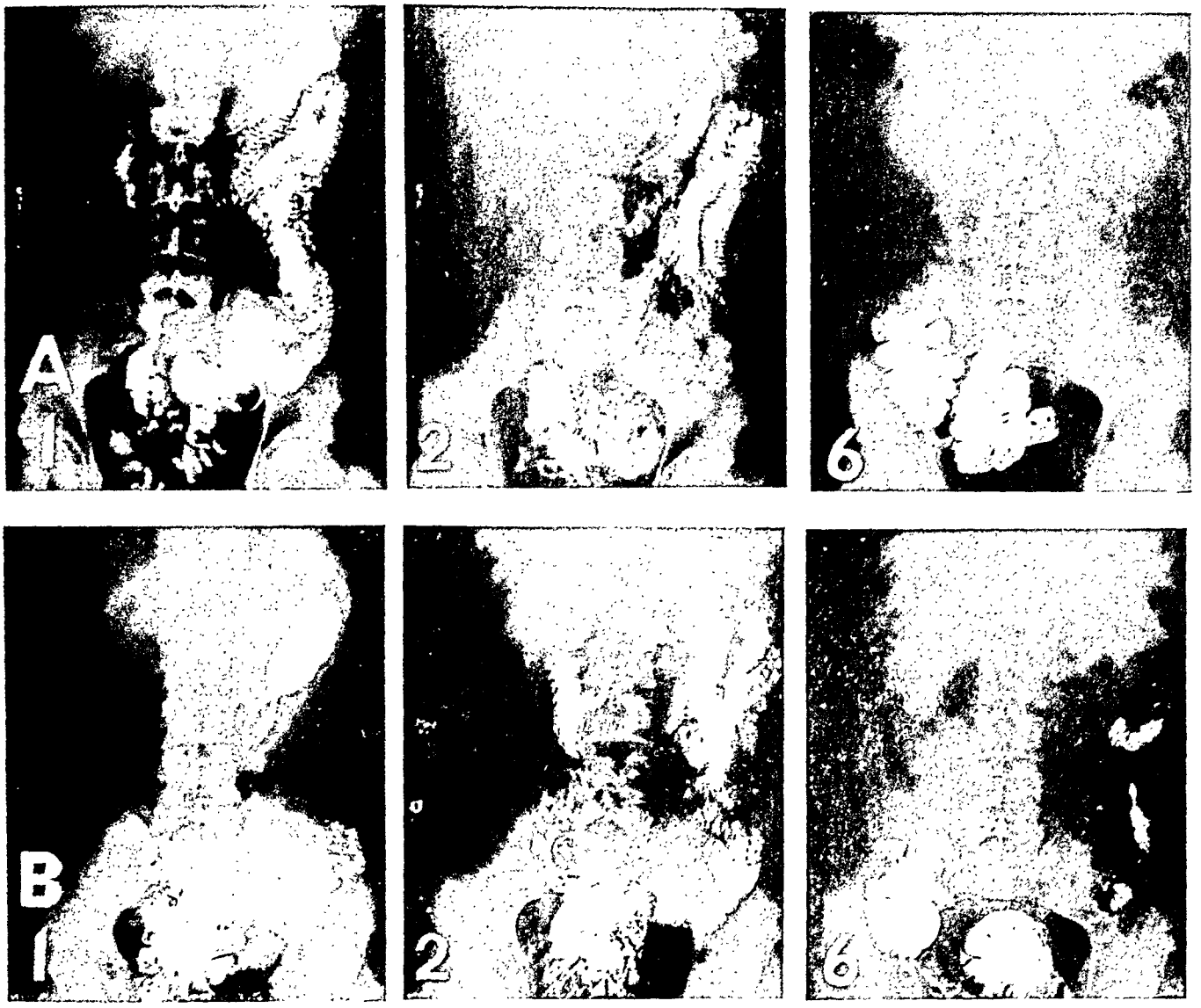


Fig. 4. — (Case 21). Roentgenograms taken at 1, 2 and 6 hours of a patient hypersensitive to egg without gastro-intestinal manifestations.
Row A. — Barium-water study showing no abnormalities.
Row B. — Barium-water-egg study showing no abnormalities.

Small bowel Studies: The barium-water test was normal. In the barium-milk study, the mucosal pattern of the stomach was normal. At one hour, the head of the barium column was in the cecum; at six hours, in the transverse colon. The upper small bowel pattern was normal. There were no changes in the ileum. The stomach was empty at the end of three hours. The transit time was two hours.

The roentgenographic findings are shown in Fig. 4 and tabulated in Table III.

DISCUSSION

That hypersensitivity to food exists and gives rise to various allergic disturbances is a well established fact, borne out particularly by the rapid relief of symptoms after the complete withdrawal of the offending food (31). The underlying mechanism of sensitization and of the resulting symptoms is unknown.

According to Ratner and co-workers (32), the mode of sensitization varies in childhood and adult life. They postulate that sensitization to food may occur in infants: (1) through the placenta by passage of undigested or unchanged protein from the maternal to the fetal circulation; (2) through the mother's milk; (3) by raw cow's milk in the neo-natal period, and (4) after acute diseases of the gastro-intestinal tract. They feel that over-feeding, "fad" diets and acute febrile and gastro-intestinal diseases may predispose adults to sensitization to food.

Walzer and associates (33), in careful and repeated passive transfer experiments, came to the conclusion that significant amounts of foreign, undigested, unchanged protein are absorbed from the gastro-intestinal tract of normal children and adults. Gutzeit (34) showed that the normal absorption is greatly accelerated and increased in the presence of gastro-enteritis or overfeeding with the protein. Hettwer and Kriz (35) found a great increase in absorp-

tion of protein from the intestinal tract if the intra-luminal pressure was raised.

Agreeing with E. Urbach (36), it may be assumed that, as a general rule, sensitization to food takes place by the penetration of abnormal amounts of undigested or inadequately digested protein through the intestinal mucosa, especially if it is damaged by inflammation, erosion or loss of mucus, or by the presence of parasites, the metabolites of which cause chronic inflammation. Allergens may be the foodstuffs themselves or the products of their incomplete breakdown to which they are reduced during digestion or by the intestinal bacterial flora, or they may be the products of the bacteria themselves.

In gastro-intestinal food hypersensitivity, the train of symptoms following the ingestion of the allergen may be elicited by two routes: (a) it may follow direct contact of the allergen with the mucosa or (b) the reaction may occur after absorption of the protein into the circulation (37). It is likely that both pathways are important in the production of roentgenographic changes. A suggestion for a possible mechanism will be presented later in this discussion.

Many authors (16, 17, 18, 38) have shown that actual gross and microscopic anatomic changes occur in the intestinal tract during the acute allergic attack. Paviot and Chevallier (39), using a gastroscope in a series of ingenious experiments, were able to observe the development of an allergic reaction in the stomach of a sensitive patient. They were impressed by the appearance of erythema, edema, hemorrhage, loss of normal mucosal folds and hypersecretion of thin, watery, non-acid mucus. Pollard and Stuart (40) reported similar findings. Gray, Harter and Walzer (41) were able to perform the passive transfer experiment on the passively sensitized mucosa of the ileum of non-sensitive patients with ileostomies and also found erythema, edema, loss of mucosal folds and hypersecretion of mucus.

The literature concerning the findings of roentgenologic importance has been reviewed earlier in this paper. Several of the findings in our patients are interesting and merit discussion.

All of the patients in group A (the food hypersensitive group with gastro-intestinal manifestations) had been studied in nearly every medical specialty clinic of the Out-Patient Department for some time. Almost without exception, they had had previous studies of the upper gastro-intestinal tract, gall bladder, colon and kidneys. All studies had been negative. All the patients at one time or another had been labeled "neurotic" by the psychiatrists.

From the roentgenographic point of view, changes in the gastric pattern and motility were less frequent than one might be led to expect from reviewing the literature. Only two patients showed convincing evidence of edema of the gastric mucosa while four of the twelve had gastric retention for six hours, which was not seen when barium alone was given.

The greatest abnormalities were present in the lower half of the small bowel where narrowing, segmentation and scattering occurred simultaneously in nearly all of the barium-food studies in group A. In the other two groups (group B and C) occasional narrowing and scattering were seen but, if present, the changes appeared in both the barium-water and barium-food series.

To be noted were: (1) the simultaneous occurrence of clinical symptoms and roentgenographic abnormalities of the small bowel after the ingestion of the allergenic food in hypersensitive patients in whom the hypersensitivity was manifested clinically in the gastro-intestinal tract; (2) the absence of symptoms and roentgenographic changes in non-sensitive persons and (3) the presence of symptoms but absence of roentgenographic abnormalities of the small bowel after the feeding of the allergenic food in hypersensitive patients in whom the sensitivity was not manifested clinically in the gastro-intestinal tract; these patients developed asthma, angioneurotic edema or neurodermatitis during or shortly after the test.

The roentgenographic abnormalities which follow the ingestion of allergenic food in sensitive patients in themselves are not diagnostic of any specific disease. Only the comparison of normal barium-water small bowel studies with examinations repeated a few days later with the offending food, in the same patient, has any significance as an aid in the diagnosis of hypersensitivity of the gastro-intestinal tract to foods. The demonstrated absence of comparable changes in the non-sensitive group (B) indicates the importance of these findings.

The mechanism underlying the changes in sensitive persons is not clear. Golden (25) has suggested that the great variety of disturbances of the motor and mucosal pattern noted in the "deficiency pattern" may be caused by the interference with the action of the intramural nerves of the bowel. Kuntz (42) considers the intramural myenteric plexi a system capable of independent, coordinated reflex activity, subject to influences from the central nervous system and directly concerned with regulation of tonus and amplitude of the intestinal musculature. Forsell (43) studied the mucosal folds grossly and histologically and is of the opinion that the size and shape of the rugae are determined by the muscularis mucosae and are adapted to segregate small boluses of chyme for easier digestion and absorption.

Biopsies of the stomach made during acute allergic attacks (18) and specimens removed at operation during similar abdominal episodes (38 a, b) show the main microscopic changes to be massive edema of the submucosal connective tissue with swelling of collagenous fibers and diapedesis of red and white blood cells. Similar changes were experimentally demonstrated by Kaiserling and Ochse (44) in the stomach of animals during anaphylactic shock.

Alvarez (45), Afendulis and Gulzow (46) and van

Liere and co-workers (47) noted that the effects of anemic anoxia on the small bowel were increasing rapidity of transit, general tonus increase and loss of coordinating power between different segments.

It thus appears that the greatly increased pressure due to edema, the stasis of blood flow with resulting anoxia and possible direct effect on the nerve fibers and cells (48) so interfere with the myenteric plexi controlling the actions of the muscularis and muscularis muscosae, that roentgenographic changes described as a "deficiency pattern" (49) follow intestinal reactions to hypersensitivity.

From the clinical point of view, the demonstration of consistent roentgenographic changes in studies of the small bowel hypersensitive to foods is important for several reasons:

1. It serves as an objective method applicable to the study of disease caused by hypersensitivity of the gastro-intestinal tract.

2. It may be used as an aid in the diagnosis of intestinal food hypersensitivity and the determination of the specific food allergen.

3. It may be used to evaluate impartially the efficacy of treatment. This aspect of the problem is now being investigated and the results will be reported in a subsequent paper. However, as heretofore, the actual diagnosis of gastro-intestinal food hypersensitivity must rest primarily on the history of intolerance to certain foods, improvement after elimination of the offending food, recurrence of symptoms after feeding of the specific allergen and the response to anti-allergic measures. The study of the small bowel, as described in this paper, should be used only as an aid in doubtful cases. It must be remembered that the roentgenographic changes resulting from administration of an allergen are not necessarily specific for food hypersensitivity and assume diagnostic significance only when a preliminary barium-water study, performed in the same patient after a sufficiently long period of elimination of the suspected offending agent, is normal.

SUMMARY

1. Survey of the pertinent literature leads us to believe that the small bowel is intimately involved in the production of symptoms in gastro-intestinal food hypersensitivity.

2. A roentgenographic approach is described, whereby changes in the small intestine in sensitive and non-sensitive patients may be evaluated under controlled conditions.

3. In a group of 12 patients with clinical gastro-intestinal food hypersensitivity, roentgenographic abnormalities of the small intestine, consisting of narrowing, segmentation and scattering, were found following the feeding of a specific barium-allergen mixture. The absence of similar significant changes in the barium-water control studies, made on the same patients, and in both the barium-water and barium-food series in non-sensitive patients indicates the importance of these findings.

4. Abnormalities of the small intestine could not be demonstrated in food hypersensitive patients whose allergic disturbances were not manifested in the gastro-intestinal tract.

5. It is worthy of emphasis that the changes described in the small bowel are, in themselves, non-specific and acquire diagnostic significance only when a comparable study without the allergen, made on the same patient after a sufficiently long elimination of the suspected food, is normal.

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Nutrition Notes

The Abuse of Alcohol

Social drinkers are persons who enjoy a moderate amount of alcoholic beverages but are never induced by any impulsion or coercion to drink steadily enough or in sufficient amounts to disrupt their personal lives, their family relationships or their economic stability. A total abstainer may be governed by a personal distaste for liquor or its effects, or influenced by the memory of a case of alcoholism in his family, or he may be activated by a fear (sometimes justifiable) of his own propensities. In some cases, therefore, a total abstainer is a potential alcoholic with a strong, self-preserving instinct. Whatever may be written about the alcoholic, one fact appears obvious — he is possessed by an insistent and usually unconscious motive of self-destruction. Not all authorities agree with this statement. If the psychiatric fraternity could evolve valid explanations for this most remarkable and deep-seated desire to perish, we might be closer to a rational explanation of alcoholism. To attribute it to such various frustrations as may be found in the individual case may not be really answering the question. Non-alcoholics will be found to be equally frustrated. Indeed, what man or woman in all history has *not* been frustrated quite seriously in the course of his or her emotional experience? The problem of the unconscious desire for death may go much deeper than even the probes of "depth psychology" can reach. In some persons the tendency to seek death via alcohol appears to be as fully integrated with their personalities as the simpler component — the taste for alcohol.

Yet the fact of alcoholism should never prevent the moderate or social drinker from his enjoyment of the taste and effects of alcoholic beverages.

Nutrition on the National and International Fronts

Nutrition was one of the six major programs adopted by the first World Health Assembly which convened at Geneva on June 24, 1948 for a four week session . . . The Latin-American Nutrition Conference was convened at Montevideo July 18-28, 1948. Some 60 persons were sent as delegates or observers from 19 countries and eight international organizations. The establishment of national nutritional organizations was high on the agenda. Nutrition surveys, determination of the nutritive value of foods already in use, orientation of agriculture to meet human physiological needs, the spreading of the fundamental principles of sound feeding, food conservation, training of nutritionists, were among the problems studied . . . A. M. A. G. supplied food for widespread child feeding and school lunches in Greece. Along with the nonfat dry milk made available to schools, necessary information as to its use also was provided . . . A special commission, appointed by the secretary of the Army to study nutrition in Bizonal Germany in May 1948 found that present food supplies do not permit increase in work output without further deterioration and the prime *desiderata* are (1) a plentiful supply of bread or potatoes, (2) proteins of animal origin and fats . . . West Virginia's "good breakfast" campaign is progressing satisfactorily . . . The Chicago Nutrition Association plans to determine the nutritional status of the people of the Chicago area and is bringing nutrition to the lay public by providing reviews of nutrition books in the daily newspapers . . . The New York City Food and Nutrition Committee has issued a leaflet "How to use dry skim milk for extra nourishment." The Queens Nutrition Committee in the next year will promote a nutrition diagnostic clinic, establish public markets, encourage greater food conservation and increase the school lunch program . . . The 16 mm., 20 minute film, "The school that learned to eat" is available from the Education Section, Dept. of Public Services, General Mills, 400 Second Ave. S., Minneapolis, Minn. It was produced for the University of Georgia with the assistance of General Mills and has been rated as the best U. S. documentary film in education.

(Nutrition News Letter Dept. Agriculture)

Publicizing the Sunshine Vitamin

The nutrition division of the Department of National Health and Welfare of Canada, with the cooperation of provincial departments of health is focusing special attention on vitamin D during 1948 and 1949. It offers continuing support to public health nurses and doctors, welfare workers and organizations in their efforts to urge parents to give their children vitamin D throughout the years of their growth.

It is not the object of the department to launch an intensive, short-lived campaign but rather to impress on parents continuously the need for regular additions of vitamin D to their children's diet. It is desired to point out that the results of rickets are far more widespread than is generally realized — one out of nine Canadian children in many areas show signs of having had the disease — and that half the children in some areas are not getting vitamin D.

Posters, exhibits, leaflets, films and film-strips — all informational media — are being used to impress on Canadian parents that their children need vitamin D every day. This material is available on request from provincial and municipal health departments.

The Brantford Experiment

For the past three years the water supply of Brantford, Ontario, has been receiving minute amounts of sodium fluoride — one part per million. Because a

whole generation of children must grow a crop of permanent teeth and careful observation be made of their dental condition during that time, the Brantford experiment will take about seven more years before results can be fully determined.

A representative group of 1800 children is being checked by the dental health division of the Department of National Health and Welfare in cooperation with Brantford health authorities and the Ontario Department of Health. Their dental condition is being compared with that of a group of 1800 children in Sarnia, where the water is fluorine-free, and in another Ontario city where the water contains natural fluorine.

Boredom as a Cause of Obesity

From personal observations as well as the medical literature, it is obvious that some individuals overeat and become adipose because of boredom. Their excesses usually are attributed to that which occasions boredom — frustration, lack of interest, hard luck, and so forth. But boredom is something additional and very much more positive. It is a rebellion against monotony — relentless, irritating, poisonous, demoralizing, insistent and provocative, whereas ennui is passive and whimsical. Much more common among the intellectually active than the torpid, boredom, like most emotional states, is unpredictable and may become chronic. It is not a condition of quiescence, but a smouldering reaction to sameness. *It is something that something has to be done about.* The presence of external impressions, repeated in unvarying cycles, leads, in the bored individual, to a desire for escape. Escape may be found along any one of many possible avenues. Eating is merely one, and it is chosen only by individuals suitably preconditioned by heredity and total life experience.

To eat is to concentrate, for the moment, upon the pure delights of taste, to enjoy the associations of a cuisine however unsophisticated, and to lose, in the adventure, the habitual state of irritation. To eat is to regain, for an instant, the elevation and dignity of one's baronial ancestors seated at their lavish board, or the ontogenetically more recent comfort of the babe at his mother's breast. The attention is diverted and a pleasant fullness obtained along with the metabolic stimulus of a specific dynamic action. But it is only the gastronomically inclined who can obtain such pleasure from a meal. In certain other types, boredom leads to fasting.

How to attack boredom, once it has been shown to be of clinical importance, is an art which requires cultivation. Change of scene, alteration of the daily routine, and the embracing of new interests are important. Unless the individual's outlook can be extended beyond his present *impasse* there is really no hope of curing his obesity. How to confer upon him an attraction to *that which is novel*, and inspire a dynamic motive of courage and resolution is part of the genius of the medical practitioner.

Abstracts on Nutrition

HUTTON, J. H. AND FALSTROM, S.: *Cholesterol-basal metabolism determinations (clinical observations in 830 cases).* Illinois Med. J., Sept. 1948, Vol. 94, No. 3, 176-179).

Owing to an alleged common belief that hypercholesteremia and low basal metabolism are reciprocal findings in thyroid deficiency, and that the blood cholesterol levels may provide a means of estimating the effects of treatment in such cases, the authors carried out the dual examinations on 830 patients suffering from a wide variety of diseases, only to discover that whereas 40 per cent of the cases had low basal metabolic readings, less than one per cent showed hypercholesteremia. The authors believe that the routine estimation of blood cholesterol is of little value in medical practice, although it probably has a place in true myxedema.

CORCORAN, A. C.: *Glycosuria: mechanism and evaluation.* (Cleveland Clinic Quart., Oct. 1948, Vol. 15, No. 4, 186-193).

The author shows that glycosuria is the result of excess of "glucose load" over renal tubular reabsorption capacity. (Glucose load is the plasma glucose content times the rate of glomerular filtration). In other words, the higher the blood sugar (arterial) and the faster the rate of filtration through the glomeruli, the larger is the load presented to the tubules for reabsorption. Excessive tubular capacity for reabsorption is the commonest cause of high renal thresholds in diabetes. In renal glycosuria there is a failure of the enzymatic process of glucose reabsorption. The author describes a method for the approximate determination of glucose reabsorptive capacity from urea clearance and concurrent blood and urine sugar.

GOODHART, R. S.: *Nutrition programs for industrial workers.* (Nutrition Reviews, Oct. 1948, Vol. 6, No. 10, 289-291).

Sufficient information is at hand to indicate that industrial workers and their families are among the less well nourished groups of the population and that special measures to improve their nutritional status are desirable. While more information is needed, it is the manifest duty of the public health worker to use his judgment and advise the most effective health measures possible with the facts and methods at hand. The National Research Council, through the Committee on Nutrition of Industrial Workers of the Food and Nutrition Board, intend to conduct a survey this year to determine the extent of in-plant

feeding and nutrition education in industry. By the spring of 1946 the Government had withdrawn from this field of work, but it is continuing, not on a war basis, but because of its importance to industrial efficiency and public health.

STEPHEN, E. H. M.: *Thiamine in pink disease.* (Med. J. Australia, July 31, 1948, 124).

The author reports excellent results in pink disease (acrodynia) from the use of thiamine, employing 10 mgm. intramuscularly every four days. Occasionally more frequent doses were required. Prior to the institution of treatment, the illnesses had varied in length from two to 12 weeks. (The author notes that some English physicians combine vitamin B_1 with liver extract with as good or possibly better results).

WILLIAMS, R. H., DAUGHADY, W. H., ROGERS, W. F., ASPER, S. P. AND TOWERY, B. T.: *Obesity and its treatment, with particular reference to the use of anorexigenic compounds.* (Ann. Int. Med., Sept. 1948, Vol. 29, No. 3, 510-532).

Some eight amino-propane compounds were investigated and it was the author's impression that the most suitable of these, considered from all aspects, was d, 1-phenyl-Z-aminopropane ("Dexedrine"). It conferred pep, ambition and euphoria and, at the same time, caused marked inhibition of appetite without producing such side-effects as apprehension, irritability and lightheadedness. However, the use of anorexigenic compounds alone does not cause sufficient loss of weight in most subjects. The usual caloric precautions and the usual psychological factors also were duly observed.

MOSSBERG, H. O.: *Basal metabolism in obesity in children.* (Nordisk Med., Sept. 24, 1948, Vol. 39, No. 39).

The basal metabolism was determined in 319 obese children and has been referred to the normal standards of Lewis, Duval and Iliff (1943). In comparison with the standard for total surface area the agreement is good with a slight trend towards low mean values regardless of the degree of over weight. The distribution is the same as that of the normal standard, ±18 per cent. The total basal metabolism of the obese children is greater than that in normal children of the same height and sex. The adipose tissue also seems to participate actively in the metabolism of the body. During puberty, children show a diminution of the annual decrease of the caloric metabolism expressed in calories per hour per square meter surface area. In comparison with the normal this change occurs earlier in obese children and at about the same time as the onset of the puberty and the prepuberal acceleration of growth of the obese children. Thyroid treatment increases the basal metabolism in the obese children.

DORAISWAMI, S. AND YUDKIN, J.: *Deficiency of vitamin A in university students.* (Brit. Med. J., Oct. 16, 1948, 708-710).

The course of dark-adaptation of 52 women university students was measured and the effect of supplements of vitamin A observed. Nine showed a significant improvement of dark-adaptation.

A study of the dietary intakes of 34 students showed that the average daily intake of seven of them was below the probable average requirement of 2,500 i. u. daily. Thus both the measurement of dark-adaptation and the assessment of the dietary intake of the vitamin reveal a similar proportion of subjects (about 20%) who were probably consuming a diet deficient in vitamin A.

Of the 13 students for whom measurements of both dark-adaptation and dietary intake were available the three whose average daily intake of vitamin A was below 2,500 i. u. were the only three whose dark-adaptation improved with vitamin A.

It is impossible to say whether the proportion of deficient subjects has been influenced by recent dietary restrictions but the fact that something like 20% of women university students were deficient in vitamin A is one which cannot be regarded lightly.

DUNNING, J. M. AND SHAW, J. H.: *Nutrition in dental education.* (Nutrition Reviews, Nov. 1948, Vol. 6, No. 11, 321-324).

Dentists ought to be trained in nutrition because the soft tissues of the mouth are among the earliest and most frequent to show signs of nutritional deficiency and because dietary control is one of the most promising ways for the prevention of dental caries. The teaching of nutrition in American and Canadian dental schools at present is fragmentary. The American Association of Dental Schools does not feel that a dentist should prescribe diets without the assistance of physicians. The authors feel otherwise and recommend extended courses in biochemistry and dietetics for practicing and research dentists.

MIRSKY, I. A.: *Emotional factors in the patient with diabetes mellitus.* (Bull. Menninger Clin., Nov. 1948, Vol. 12, No. 6, 187-194).

In a wide-angle view of the etiology of diabetes, the author places hereditary predisposition at the top of the list, so that some persons may be said to begin their diabetes at birth, although other precipitating factors may be necessary to render the disease apparent. Among these, of course, is adiposity and infection. In any case, there is a profound disturbance of the intracellular enzyme systems, the exact nature of which is not too well understood. Emotional factors appear to be of importance as precipitating factors in those hereditarily predisposed. The tensions produced by the activation of repressed unconscious conflicts, seek indirect expression through the vegetative nervous system. It is only when trauma reactivates some infantile neurosis and thus releases more primitive patterns that sufficient stress is developed

to produce or precipitate diabetes mellitus. It is quite possible that such serious stress, if continued, might supply the "noxa" for Selye's formula of the Adaptation Syndrome, eventually resulting in diabetic mellitus.

BENEDEK, T.: *An approach to the study of the diabetic.* (Psychosom. Med., Sept.-Oct. 1948, Vol. X, No. 5, 284-287).

This article, cast in the jargon of the psychologists, is difficult to assess, but obviously important enough that the attempt should be made. Its main import is the creation of a method of approach to the study of the psychology of diabetics. At present the authoress has nine diabetics under strict observation and analytical investigation. "Free dieting" *a la Tolstoi* is employed. An effort is made to trace correlations between emotional fluctuations and metabolic reactions. An effort is also made to detect behavioral changes that arise from the patient's perception of metabolic dysfunction. A search is undertaken for some basic biological pattern or "instinctual constellation" predisposing the patient to diabetes should precipitating factors occur. She feels that an increase in the rate of the breakdown of liver glycogen is to be regarded as an *unconsciously functioning emergency response* of the diabetic. Being told that he has diabetes is definitely traumatic to the individual. The first (and almost general) reaction to the recommendation of a free diet is the mobilization of anxiety, the patient developing a sense of being unprotected. Insulin sometimes becomes the tool for mastering anxiety, a source of gratification and a symbol of power.

DANIELS, G. E.: *The role of emotion in the onset and course of diabetes.* (Psychosomatic Med., Sept.-Oct. 1948, Vol. X, No. 5, 288-290).

It is definitely established that emotions play a role in the fluctuation of blood sugar levels in diabetes and there is some accumulating evidence that emotions may at times play a role in precipitating the disease. Theoretically the anterior pituitary gland might play an important part in such a mechanism, although there is no proof that it does.

TOLSTOI, EDWARD: *The objectives of modern diabetic care.* (Psychosomatic Med. Sept.-Oct. 1948, Vol. X, No. 5, 291-294).

The author here reviews his own personal attitudes in the treatment of diabetics and, after a decade of "free-dieting" along with limited doses of insulin, sees no reason to alter his course because no one as yet has been able to show that glycosuria or hyperglycemia are responsible for the complications of diabetes. Tolstoi's patients have allegedly done just as well as those treated by the methods of the "chemical" school and they have been incomparably freer of worry.

Editorial

Submicroscopic Spherical Bodies Found in Human Cancer

THE ELECTRON MICROSCOPE is one of many new instruments which have been developed during the past few years. This new device makes it possible to peer into such minute details as were hardly dreamed of in former times. The direct magnification with the electron microscope is between 800 and 25,000, as compared with the 1,200 when a microscope is used. Electron micrographs are often enlarged up to 200,000 magnification revealing more and more details, so that even viruses have become visible. However, as with all new developments, new methods have to be devised to make the greatest possible use of them. The average slice of tissue is too heavy for the electron microscope, therefore, Fullam and Grey had to devise a special machine, a high speed microtome, which furnishes material to be analyzed under the electron microscope. Then, came the question, how to localize a minute portion of the tissue for this tremendous enlargement. The same authors constructed a Specimen Punch, which can be attached to a microscope. The fixation of the material to be examined is also a special process. The "Grey fixation" is an elaborate process using different agents, such as formalin, osmium tetroxide, potassium dichromate and chromic acid.

Only after these technical problems had been overcome, the real work of examination of tissues under the electron microscope could be undertaken. The reports of the studies of Gessler, Grey and McCarthy are now published in Experimental Medicine and Surgery and are startling. Working in the Research Laboratories of the Interchemical Corporation, they studied tissues obtained from the pathological laboratories of the New York Post Graduate Hospital. Only in carcinoma specimens did they find under the electron microscope, dense, submicroscopic bodies of more or less spherical shape. None of the healthy tissues showed these bodies in spite of extensive control examinations.

Gessler, Grey and McCarthy think that these bodies are of endogenous origin and specific for cancer. The bodies vary to a considerable extent in size. They possess diameters from 800 to 1500 Angstroms. They occur in isolated units, in pairs, groups, chains or in clusters. The bodies are distinguished by their high density, either in the sense of greater opacity to the electron beam, or, of specific gravity, which seems to be higher than that of other cellular parts of similar size. The distribution of these bodies is not uniform throughout a given tissue. The authors found them within epithelial cells as well as in parts of connective tissue, where they seem to occur fre-

quently in their highest concentration.

When the bodies appear within cells, the latter frequently display signs of disintegration. Under the electron microscope their nuclear membranes and nuclear contents appear to be affected and often broken. These dense bodies not only appear in sections of the tumor, but, what is of the greatest importance, frequently in sections of tissue considerably remote from the tumor site.

Gregory, in another article in the same issue of Experimental Medicine and Surgery, confirms Gessler's findings. He considers the spherical bodies to be virus-like. He found that when left at room temperature for a certain time, the bodies lose clear-cut details. These bodies were cultured in the egg with considerable ease. In four day egg cultures, these spherical bodies were much more concentrated than in the original specimen. Gregory thinks that these bodies have all the characteristics of a virus: distinct cellular characteristics, cell wall, cytoplasm and nuclei. He even states that they multiply by cellular division. Therefore, he concludes that it is probable that these bodies are the cancer virus.

We are only too well aware that in spite of the tremendous effort and money spent on research to determine the cause of cancer, very little has been found to date. However, it seems that through the application of the electron microscope, an entire new field has been opened to science. We are unable to decide whether these bodies detected in cancer are really viruses or other metabolic substances, and what role they play in the growth of pathological studies.

One of the findings appears to us of the greatest value for the future:- the detection of these spherical bodies in tissues far away from the original site of the tumor.

If these findings should be substantiated in further studies, it would be possible to detect an internal cancer by examination of some superficial tissue, which is easily accessible. It is too early to speculate over all the possible consequences of Gessler's discoveries. We consider his work and that of his colleagues of the utmost importance, as it indicates a stimulating approach to the studies of malignancy; and possibly actual progress in this resistant field.

FRANZ J. LUST, M.D.

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The International Academy of Proctology

THE GASTROENTEROLOGIST and the proctologist meet on common ground in the colon. Both are concerned about the diagnostic and therapeutic aspects of colon disease. The gastroenterologist employs the sigmoidoscope as regularly as does the proctologist.

The formation of the International Academy of Proctology is thus of equal interest to the gastroenterologist and the proctologist.

The International Academy of Proctology was founded July 6, 1948, for the following purposes:

To unite in one association physicians who are engaged in the specialty of Proctology or its allied fields.

To advance the practice and study of diseases of the colon and accessory organs of digestion, including those of nutrition.

To stimulate and encourage research in proctology.

To promote the practical application of all recent advances in proctology and to help correlate clinical and experimental studies.

To keep a record of all medical institutions in which proctology and allied subjects are taught, with full data pertaining to them; to encourage instruction in proctology as a specialty, as well as in subjects allied to proctology; to establish chapters or branches of this Academy in various parts of the country; and, to conduct clinical meetings in proctological subjects independently or in conjunction with other medical organizations.

To formulate the highest standards and principles for the practice of proctology.

To encourage legislation and public support for the advancement of proctology.

To edit and publish the proceedings of the Academy, and all matters, papers, articles, subjects and reports considered by the Academy.

To act as a control agency through which all qualifications and all requirements relating to the specialty may be standardized.

These are the objectives of the International Academy of Proctology as indicated in the Certificate of Incorporation presented to the University of the State of New York.

The operation of the Academy shall be conducted principally within the United States and its territories and generally throughout the world.

The existing proctological associations are limited in membership and scope. It is our object to be International in scope, extensive in membership, and active in the development of high ideals for the specialty of proctology. It is our further objective to establish standards for qualification, and our own Board for qualification of proctologists.

The Academy will support the American Medical

Association in its high ideals.

The Academy is composed of Members and Fellows, who belong to its constituent chapters or who have joined the International Academy directly from a locality where a chapter does not exist.

Members are defined as physicians engaged in the practice of medicine whose interest lies in the field of proctology, but who are not necessarily limited to this specialty. Applicants must possess the M.D. degree, and must be members of their state and county medical society in the United States (or equivalent organizations in foreign countries).

Fellows include Honorary Fellows, and Associate Fellows.

Honorary Fellows are physicians engaged in or wholly interested in the specialty of proctology, or allied subjects, whose outstanding achievements in their specialty or practice particularly merit such distinctive honor. These physicians are approved by the International Committee on Membership and submitted for election by a majority vote at the annual meeting of the International Academy.

Fellows are physicians whose achievements in proctology warrant this honor, or who are diplomates of the American Board of Surgery or Board of Proctology, or if living in a foreign country where such a qualifying board or organization does not exist shall submit qualifications of an equal standard.

Associate Fellows are physicians engaged in proctology or an allied specialty whose achievements in their own specialty warrant distinctive honor and whose interest in proctology is keen and progressive.

Thus, it is evident that the requirements for membership are high but simple. Experience, study and achievements are accorded proper recognition and are acceptable in lieu of more formal training where indicated. Although standards are high, membership will not be limited to a small clique.

The establishment of this new organization is a milestone in the development of Proctology. Inasmuch as the gastroenterologist is, in essence, a diagnostic proctologist as well as enterologist, he would be qualified for affiliation with the Academy. Thus, every proctologist and gastroenterologist owes it to himself, and to the advancement of his specialty, to qualify for membership in the International Academy of Proctology.

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Book Reviews

EXPERIMENTAL IMMUNOCHEMISTRY. By Elvin A. Kabat, Ph.D. and Manfred M. Mayer, Ph.D., 567 pp. Charles C. Thomas, Springfield, Ill., 1948, $8.75.

The fascinating feature of this delightful and enlightening volume is the application and uses of quantitative immunological methods. Precipitin reactions, agglutination, complement fixation, allergy, anaphylaxis and antibodies all receive due treatment. Today, the immunologist is in possession of a store of marked molecules, each as individually marked as if it contained a radioactive tracer element. One section of the book deals with the preparation of well characterized individual proteins, enzymes, specific polysaccharides and related material. While the book will add to any physician's knowledge of an increasingly complex phase of medicine, it actually will serve as a laboratory manual for the immunologist.

THE SURGERY OF THE STOMACH AND DUODENUM. *By T. H. Somervell,* M.A., M.B., etc. pp. 546 ($11.00). The Williams and Wilkins Co., Baltimore, 1948.

This is a compressed but satisfactory and highly readable dissertation upon diseases of the stomach and duodenum with detailed descriptions of their surgical treatment. The English style of the author is excellent. The illustrations, quality of paper, and general format leave nothing to be desired. The book is recommended to the surgeon who desires to imbibe the viewpoints and attitudes of an English surgeon now working in India, and who, through his knowledge of art, has made all his own illustrations.

THE MODERN MANAGEMENT OF GASTRIC AND DUODENAL ULCER. Edited by F. Croxon Deller, M.D., pp. 227, ($5.50). The Williams and Wilkins Co., Baltimore, 1948.

This volume is the work of several London physicians and surgeons and covers the subject in a compact manner, dealing with the surgical as well as the medical treatment of peptic ulcer. The etiological factors are presented with due skepticism as to the validity of each or all of them. The section on diagnosis is particularly valuable. Sir Arthur Hurst's dietetic measures are presented in some detail. The attitude of these English authors with respect to vagotomy, subtotal gastrectomy and indeed all aspects of peptic ulcer shows no significant deviation from the average American attitude today. We recommend the book to all physicians and surgeons.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN
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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

SAUNDERS, G. C.: *Black hairy tongue.* (Northwest Med., Oct. 1948, V. 47, No. 10, 744-745).

The condition known as black hairy tongue is usually asymptomatic and encountered in routine examinations. The black mass extends forward in the midline from the angle of the circumvallate papillae on the upper surface of the tongue and suggests a tuft of black hairs. Microscopic examination of the "hairs" shows an incomplete core of connective tissue caused by epithelial cells resembling those of the rete malpighii but in many the center of the filament consists entirely of flattened, keratinized, non-nuclear cells. No etiological factor has been found. The best known treatment is vigorous daily scrubbing with a stiff tooth brush, as this keeps it under control. The condition has no effect on health and apparently tells us nothing about the health of the patient possessing it.

STOMACH

OSTRUM, HERMAN W. AND SERBER, WILLIAM: *Tuberculosis of the stomach and duodenum.* (Am. J. Rad. Therapy. 60, 3, 315. Sept. 1948.

Two cases of tuberculosis of the stomach and one of the duodenum are described. In all three cases the lungs showed no active pulmonary tuberculosis. One patient had a peripheral tuberculous adenitis for years, and in all three cases abdominal lymph node involvement was a very prominent feature. All three patients developed perforations or fistulous tracts at the site of their lesions. From the roentgenological standpoint there are no pathognomonic findings. The ulcerative and infiltrative lesions can easily be confused with benign ulcer or carcinoma. A combination of both types of lesions, as well as extensive mucosal nodularity, might be suggestive. The most significant findings that can be demonstrated roentgenologically are simultaneous involvement of the stomach and duodenum, the presence of fistulae or sinuses, and signs of external pressure by enlarged lymph nodes.

FRANZ J. LUST

PALMER, E. D.: *Observations on the treatment of chronic hypertrophic gastritis with shortwave diathermy.* (Rev. Gastroent., March 1948, Vol. 15. No. 3, 233-241).

Briefly, a study of 30 hospitalized patients with chronic hypertrophic gastritis, showed that short wave diathermy, as here applied, (over the epigastrium) had no significant therapeutic effect on the clinical or gastroscopic course of the disease.

IRVINE, W. T.: *Post-prandial symptoms following partial gastrectomy.* (Brit. Med. J., Sept. 11, 1948, 514-515).

The attacks of giddiness, sweating, palpitation, "hotness" and even vomiting which appear post-prandially soon after partial gastrectomy in many patients have, as a rule, hitherto been attributed to the "dumping" mechanism, whereby a rapidly emptying stomach produces a sudden hyperglycemia followed shortly by a compensatory low blood sugar. Dr. Irvine, however, has convincingly shown that this is not the true explanation, and that distention of the gut is the actual cause. In 24 cases, all of whom showed the unpleasant symptoms, the attacks invariably occurred during the period of elevated blood sugar. Furthermore, the severity of the attack was definitely related to the *bulk* of the meal. The inference from this work is that the attacks may be avoided by reducing the bulk of the meals.

PALMER, EDDY D.: *The gastroscopic picture in post-irradiation gastritis.* (Am. J. Roent. Rad. Therapy. 60, 360. September 1948).

Gastroscopic studies in twelve patients who had developed post irradiation gastritis following intensive radiation treatment for malignant disease showed remarkably constant and characteristic gastric changes. The picture included marked edema with tubular deformity and fixation of the antrum, similar fixed patulousness of the pylorus, and clean deep chronic ulcers which healed without contracture. Following subtotal gastrectomy with posterior gastroenterostomy, the picture was that of normal postoperative stomach. Pathologic and roentgenographic studies in general corroborated the gastroscopic findings. A new gastroscopic entity is presented, but, because the diagnosis of post irradiation gastritis should be obvious from the history, the importance of endoscopy lies in the evaluation of the severity of the radiation damage.

FRANZ J. LUST

BOWEL

RICKETTS, WILLIAM E., KIRSNER, JOSEPH B., AND PALMER, WALTER LINCOLN: *Chronic non-specific ulcerative colitis.* (Gastroenterology 10, 1, 1-15. January 1948).

The presence of an apparently normal colon by

X-ray examination in 60 of 156 patients with typical clinical evidence of non-specific ulcerative colitis indicates clearly that the disease may remain a relatively superficial process, anatomically, in many patients with symptoms of long duration.

The demonstration of involvement of the entire colon in 22 patients with symptoms of less than one years duration is of particular interest. In fact, in 15, symptoms had been present for less than six months. These roentgenologic findings correspond with the clinical observations made in another study, demonstrating that the mortality rate is highest in the first one or two years of the disease. In the present series no significant change was found during the time of observation in 65%. The evidence thus suggests that, in the majority of cases, the disease attacks the colon either partially or completely during the initial episode and usually remains relatively stationary thereafter.

Although roentgen evidence of progression was obtained in 24%, retrograde extension of the disease from the rectum to the ileocecal valve was noted in only one patient. There were slight changes in the mucosa of the entire colon, initially in another patient. Four months later the recto-sigmoid and the descending colon appeared definitely narrowed and rigid, and two years after the original examination the disease had extended to the transverse colon. In a third patient, the initial barium enema, six months after the onset of symptoms, disclosed an absence of haustra in the descending colon and only partial loss of haustra in the remainder of the large bowel. Six years later the entire colon appeared to be rigid, contracted and devoid of haustrations. Similar findings were noted in five other patients of this group. It would appear, therefore, that progression of the disease often consists of an increase in the severity of the changes in segments already involved, rather than continued retrograde extension of the process.

The chronicity of the disease is indicated by the fact that definite roentgenologic evidence of regression was obtained in only 11% of the cases studied. Nevertheless, it is to be noted that the colon in two patients with previously demonstrated total involvement regained a normal appearance.

FRANZ J. LUST

KLINE, J. R. AND CULVER, G. J.: *Roentgen findings in primary duodenal and paraduodenal malignant lesions.* A. J. Roentgen. and Rad. Therapy 58, 4, 425. October 1947.

The difficulty in finding non-obstructing malignant tumors in and around the duodenum is well known. Only careful examination and especially careful study of the mucosa of the duodenum enables us to make a diagnosis. It is important to go over the films of the two reported cases of carcinoma of the papilla Vateri, to understand the difficulties of the authors in evaluating them. Besides, Kline and Culver show the roentgenogram of the rare case of a carcinoma of the second portion of the duodenum, which can be compared with a drawing of the specimen. The fourth case is that of a benign cyst of the head of the pancreas, producing a wide duodenal sweep and pressure effect on the mucosa of the duodenum.

In coming to a final diagnosis all clinical and laboratory findings have to be taken in account.

FRANZ J. LUST

CRIDE, R. H., ROSENBAUM, M., AND FERRIS, E. B.: *Amebic colitis.* (Psychosomatic Med., July-August, 1948, Vol. X, No. 4, 223-229).

The case is presented of a young ex-soldier who developed amebic colitis in Guadalcanal and in whom subsequent attacks of diarrhea coincided with periods of unusual emotional stress. Personal history revealed a dominating mother who habitually took an unusual degree of interest in the patient's bowel movements when he was a child. Dr. Rosenbaum, while giving due credit to the amebic dysentery for symptoms, felt that the patient had been rendered unduly bowel conscious, to such a degree that almost any form of emotional stress would precipitate diarrhea even independently of the organic disease. The patient was the only person of several who developed the organic disease after drinking from a polluted stream, and this fact suggests that his "colonic" emotional pattern may have predisposed him to acquiring the infestation in the first place.

BELL, J.C. AND DOUGLAS, J. B.: *Roentgen-ray diagnosis of malignant and potentially malignant lesions of the colon and rectum* (Radiology, Sept. 1948, Vol. 51, No. 3, 297-304).

The authors point out that since patients now are presenting themselves much earlier in carcinoma, the diagnostic difficulties are thereby increased. Their technique for X-ray examination of the colon is detailed. In a large series of cases slightly more than 50 per cent with operable lesions are living and free from demonstrable cancer at the end of five years. If diagnosis can be made before lymph node involvement takes place, we can anticipate an increase of at least ten per cent in those well at the end of five years.

"In cancer of what other organ," they ask, "can better results be shown?"

BLACK, W. R.: *The role of abdominal trauma in acute appendicitis.* (Brit. Med. J., Aug. 28, 1948, 424-425).

Two children are described in whom acute appendicitis quickly developed following minor types of abdominal traumata. The appendix in each case contained a fecalith near the base with foul muco-purulent material distally. Theoretically, even a minor trauma might dislodge a fecalith and cause it to block the drainage of the appendix thus causing the attack. Such cases might have a medico-legal significance where the injury was incurred in line of work and compensation sought in the courts.

POWELL, R. A.: *Partial small bowel obstruc-*

tion due to metastatic carcinoma secondary to squamous cell carcinoma of the cervix uteri. (Alex. Blain Hosp. Bull., Aug. 1948, Vol. 7, No. 3, 81-84).

The case mentioned in the title was successfully treated surgically. The author could find only two other cases in the literature of the past 10 years. His case may represent an instance of a localized metastasis due to direct implantation of the malignant cells, occurring at the time of the surgical attack on the primary lesion of the uterine cervix. Only 10 months intervened between the two operations.

LÖVGREN, D. AND TÖRNQUIST, S.: *Isolated lymphogranulomatosis in the intestinal canal.* (Nordisk Med., Aug. 13, 1948, Vol. 39, No. 33, 1505-1506).

Three cases are described of isolated lymphogranulomatosis in the intestinal canal, all of whom were subjected to operation. One lived a year and a half while the other two are still living and well after 4 1/2 and 13 years respectively. Lymphogranulomatosis localized to the intestinal canal apparently carries a much better prognosis than the general form.

KATTERJOHN, J. C.: *Carcinoma of the colon simulating carcinoma of the stomach.* (Radiology, August 1948, Vol. 51, No. 2, 245-247).

Two cases are reported in which the roentgen appearances suggested strongly cancer of the stomach, although in both cases the malignant lesion was in the transverse colon. In one case the lesion actually involved the stomach. In the other, the colonic lesion had no attachment to the stomach but was held firmly against the gastric wall by an adhesion between the colon and the duodenum. The gastric deformity was apparent only, and not real. From this experience it would seem that good practice might include an X-ray examination of the colon when one finds a gastric lesion on the greater curvature, and on X-ray examination of the stomach in cases having a carcinoma of the transverse colon in a region where gastric or duodenal involvement might occur.

COTTER, W. M. AND GEBBIE, I.: *Appendicitis in retreat.* (New Zealand Med. J., June 1948, Vol. 47, No. 259, 225-228).

The treatment of appendicitis has been changing. Formerly "the attack had the vigor, urgency and simplicity of a cavalry charge." Sometimes we may now profit by delay, since we have new weapons — a better understanding of intravenous fluids, the sulfonamides and penicillin. The author shows that between 1925 and 1947 there has been a fall in mortality from appendicitis from 17 per cent to five per cent. The author praises the use of the McBurney incision, also the expectant treatment of localized appendicitis as factors helping to cause the improved death rate.

CHIPPS, H. D.: *Oxyurids in the appendix.* (Northwestern Med., Sept. 1948, Vol. 47, No. 9).

The general opinion is held that the presence of pin-worms in the appendix is not etiologically related to acute appendicitis, but the author reports an incidence of 10.7 per cent in 375 surgically removed appendices. In children twelve years old or younger the incidence was 34.4 per cent. Although surgical intervention was justified in 71 per cent of the cases on clinical grounds, only two of the 40 cases were diagnosed pathologically as acute appendicitis, the others being essentially normal except for the worm content. The problem of oxyuriasis of the appendix simulating acute appendicitis is chiefly a pediatric one.

WYATT, G. M.: *Barium sulfate in saline suspension: examination of the colon in the presence of partial obstruction.* (Radiology. Sept. 1948, Vol. 51, No. 3, 326-330).

The mixing of a saline cathartic with barium to be orally administered is rarely indicated. But there is a small group of patients presenting the picture of obstruction of the colon to the passage of a barium enema without clinical obstruction. In these patients the use of a saline cathartic will prevent dehydration and impaction of the barium and allow examination of the colon with barium by mouth.

PANCREAS

EPSTEIN, B. S. AND ISAACS, I.: *Calcareous pancreatitis.* (Radiology, August 1948, Vol. 51, No. 2, 214-218).

The case is presented of a 39 year old woman with acute and chronic diffuse calcareous pancreatitis. Biopsy during the relatively acute stage of the disease showed acute and chronic inflammatory changes. At that time arcuate impressions in the distal portion of the transverse colon and the greater curvature of the stomach, due to enlargement of the pancreas, were seen, and several small calcific deposits were present in the head and body of the pancreas. As the acute phase subsided, the pancreatic calcification increased visibly in one month and after ten months the entire organ was infiltrated with lime salt.

REEVES, R. J. AND MORAN, F. T.: *Diffuse pancreatic calcification: an analysis of six cases.* (Radiology, August 1948, Vol. 51, No. 2, 219-224).

Six cases of diffuse pancreatic calcification are described, five of whom were adults whose chief complaint was recurring abdominal pain of over two years duration. The sixth case was that of a four year old girl, believed to be one of the youngest patients with calcified acquired pancreatic disease on record. Among possible etiological factors was heavy alcohol consumption in two and cholelithiasis in a third. Complications included steatorrhea, diabetes mellitus, pain and drug addiction. Surgical treatment includes removal of localized concretions, partial and complete pancreatectomy, and celiac ganglionectomy for pain relief.

ABRAMSON, L.: *Sympathectomy to relieve pain in pancreatolithiasis.* (Nordisk Med., Aug. 13, 1948, Vol. 39, No. 33, 1506-1507).

In pancreatic calculus pain may be severe enough to render the patient an invalid. One way of combatting this pain is by partial or complete interruption of the sympathetic nerve paths of the pancreas. A case is described in which left-sided sympathectomy gave considerable, though not complete relief from pain.

LIVER AND GALLBLADDER

AYER, A. A. AND THANGAVELU, M.: *Congenital anomaly of the liver.* (J. Indian Med. Assn., June 1948, Vol. 17, No. 9, 291-293).

At an autopsy on a male subject, aged 40, a congenital anomalous condition of the liver was noted. The left lobe was relatively very large and the right lobe diminutive in size. There was extra lobulation of the left and quadrate lobes caused by fissures reminiscent of some of the fissures of the fetal liver. There was a complete division of the liver into two fragments by a continuous cleavage line representing the fissure at the site of the fossa for the gall bladder, running into the *porta hepatis* and further continuing into the fissure at the site of the ligamentum venosum. The right fragment included the blended right lobe and spigelian lobe and the left fragment represented the fused left lobe and quadrate lobe. A condition homologous to this is seen in the liver of an old world monkey, *Semnopithecus entellus*, in which the liver is similarly and correspondingly divided into two fragments.

PORTEOUS, W. M.: *Hepatitis in New Zealand.* Med. J., June 1948, Vol. 47, No. 259, 201-213).

Porteous finds that hepatitis in New Zealand has become, in recent years, a disease of major importance and increasing incidence. The native Maoris enjoy a relative immunity to the virus of infective hepatitis. In a series of 15 cases of subacute and chronic hepatitis, he found that eight were of rapid onset and seven of insidious onset. In the latter group women greatly outnumbered men (six to one). Alcohol was a possible causal factor in only one case while malnutrition was not evident. Both these groups are probably of infective origin. In a total series of 45 cases, several idiopathic cases were encountered. Some acute cases rapidly develop "acute yellow atrophy" and die. Again, some acute and some subacute cases of hepatitis occur without jaundice. Biopsy of liver was used in some cases as a diagnostic aid.

PHYSIOLOGY

DOUGLAS, G. F. JR., AND PRATT, T. D.: *Fat and nitrogen absorption after folic acid.* (Proc. Soc. Exptl. Biol. Med., V. 68, p. 171, 1948).

The pancreatic ducts were ligated and the pancreas left in situ in dogs. Fat absorption and protein absorption became depressed because of the faulty digestion. Administration of folic acid did not increase absorption of either fat or nitrogenous material, contrary to the expected findings from the work of Spies and associates.

The authors find that using the per cent of fat in the stool as an index of fat absorption is extremely unreliable. They believe that fecal fat must be correlated with dietary fat in order to evaluate the absorption of the latter.

Propeptan Therapy for Gastro-Intestinal Food Hypersensitivity

By

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A FEW REPORTS have been made (1) describing an objective method of demonstrating changes in the gastro-intestinal tract of persons suffering from food hypersensitivity. Using this procedure, we have evaluated the results obtained by the use of type-specific food digests, called propeptans, (2) in the treatment of food hypersensitivity.

HISTORY

Magendie (3) (1839), and later Theobold Smith (4), noted the hypersensitivity reaction in animals, while C. Richet (5) (1902) published the first detailed study of the subject and coined the word "anaphylaxis." Arthus (6) (1903) described "local anaphylaxis" and stressed the strict specificity of the reaction. On the suggestion of C. Richet (5), who had found hematemesis, diarrhea and melena to be salient features of anaphylactic shock in dogs, LaRoche, C. Richet, Jr. and St. Girons (7) investigated alimentary hypersensitivity. They concluded that the reaction could be acute or chronic and could involve the cutaneous, alimentary, respiratory or nervous systems. They noted that "the symptoms were always of the same type in the same patient, but could be different in different patients sensitive to the same foods and that similar symptoms in the same patient could be due to different foods."

Besredka (8) (1908) demonstrated that previous oral or hypodermic adminstration of minute, sublethal quantities of anaphylactic substance gave temporary protection against otherwise uniformly occurring anaphylactic shock. He was able completely and permanently to eliminate anaphylactic shock by this treatment. As a result of his investigations, he came to the following conclusions: (1) Since the anaphylactic state is apparently due to a specific cellular sessile antibody, it can be neutralized by a series of graduated small injections (or oral administrations) of the antigen neutralizing the sum total of the antibodies present (2). Antianaphylactic immunity depends upon the slow neutralization of the antibody by the antigen (3). Anaphylactic shock is also a form of desensitization, only it is rapid (4). The speed of combination of the antigen and antibody governs the speed of the reaction. Richet (9) and Grineff (10) later confirmed these findings of Besredka. Lambert and associates (11) coined the term "skeptophylaxis" (sudden protection) for this type of specific therapy.

Dreyfuss and Lesne (12) showed that the administration of predigested foods caused the loss of their sensitizing and anaphylactic powers. Auld (13) and Dale (14) noted that hypodermic administration of commercial (Witte) peptone resulted in a non-specific reduction of sensitivity. However, the parenteral administration of peptone was fraught with the danger of sensitization to the peptone and subsequent peptone shock. Pagnier and Vallery-Radot (15), therefore, administered commercial peptone orally to patients suffering from urticaria and angioneurotic edema due to food hypersensitivity and obtained satisfactory results. Luithlen (16), while unable to confirm the results of Pagnier and Vallery-Radot, felt that type-specific digestion products should be used to produce the desired skeptophylactic effect. He found that the digestion of protein could be carried past the proteose level without loss of specificity. He prepared type-specific protein digests, since the commercial "peptone" consisted principally of metaprotein and proteoses, and was prone to produce untoward reactions. Unfortunately, Luithlen died shortly after making this discovery without completing his investigations.

E. Urbach (2) demonstrated that specific protein digests, called propeptans, when administered orally, had a skeptophylactic effect in food hypersensitivity and that they would produce permanent desensitization. Many authors (17) have reported satisfactory clinical results following the proper administration of propeptans.

MATERIAL

As several reports have shown (1), roentgenographically demonstrable and reproducible changes occur in the gastro-intestinal tract of patients suffering from food-hypersensitivity. Tallant, and coworkers (1e) stated that these changes probably occur only if the signs and symptoms of sensitivity are manifested in the gastro-intestinal tract. This method of investigation permits an objective demonstration of the efficacy or lack of efficacy of any given procedure for the treatment of food-hypersensitivity, provided the clinical symptoms occur in the gastro-intestinal tract of the patient being investigated.

All the patients who were treated with propeptans in the manner to be described later, had been studied in either the hospital or out-patient department and gave histories of food-hypersensitivity with severe gastro-intestinal manifestations. No abnormalities were found on physical examination. Roentgenographic examinations of the gastro-intestinal tract and gall bladder, performed in the routine manner, were normal

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in all. All showed clinical improvement after complete elimination of the offending foods and exacerbation of their symptoms followed the subsequent administration of the offending foods.

As it has long been known that psychiatric disturbances greatly accentuate allergic symptoms (18), two groups of patients were studied:

Group A. Seven patients with personal and family histories, clinical symptoms and roentgenographic evidence by controlled studies of the small bowel (1e), of severe food-hypersensitivity, but without psychiatric disturbances.

Group B. Three patients with long-standing psychiatric disturbances in addition to the criteria listed under Group A.

TECHNIC

Preliminary roentgenographic examinations of the small bowel were performed in the manner previously described (1e). Two separate studies of the small bowel were made before beginning treatment with propeptans. The first was performed after the suspected food had been eliminated completely from the diet for five days, using pure barium sulfate and water as the contrast medium, and gave a normal result in all cases. The second was performed five or more days after the first study and the food to which the patient was clinically hypersensitive was added to the barium sulfate-water contrast medium. This second procedure gave significantly abnormal results in all the patients.

Following the preliminary series of roentgenographic examinations, a strict "propeptan diet," as described by E. Urbach (19a), was given to each patient. The patient received 0.1 Gm. of type-specific propeptan* in capsule form exactly 45 minutes before each meal and the food to which the patient was being desensitized was eliminated from the diet. When there was hypersensitivity to several foods, the patient received one capsule of each 45 minutes before meals. At the end of three days, when it had been determined that the propeptan alone had not produced any untoward clinical manifestations, the smallest amount of the offending food which the patient was known to tolerate without symptoms was added to each of the meals. After three to five days, if no symptoms had developed the amount of the offending food was increased by adding 20 to 25 per cent every three to five days, until the patient was ingesting average normal quantities of the food without discomfort.

If the patient, at any time, complained of distress during this regime, the largest amount of the food previously tolerated without distress was given for one week. The amount was then slowly and carefully increased.

When the patient could tolerate average normal quantities of the incriminated food without distress, that quantity was given for one to two weeks. The propeptan capsules taken daily were then gradually reduced until, at the end of two to three weeks, they were entirely eliminated.

The treatment of a patient hypersensitive to milk (case 4) is given in detail in Table I.

At the end of approximately five weeks of treatment, roentgenographic examination of the small bowel was repeated, using barium, water and the previously offending food as the contrast medium. This series was then simultaneously compared with the previous abnormal study of the small bowel, using an 8-section view box.

RESULTS

Before the results of treatment can be discussed, certain terms used in the description of the roentgenographic studies must be defined.

TABLE I.

Propeptan Treatment of a Patient Hypersensitive to Milk. (Case 4)

Day of Treatment	Breakfast Amount Propeptan (Gram)	Breakfast Quantity of Milk (fl. oz.)	Luncheon Amount Propeptan (Gram)	Luncheon Quantity of Milk (fl. oz.)	Dinner Amount Propeptan (Gram)	Dinner Quantity of Milk (fl. oz.)
1-4	0.2	0	0.2	0	0.2	0
5-8	0.2	1/4	0.2	0	0.2	1/4
9-13	0.2	1/4	0.2	1/8	0.2	1/4
14-16	0.2	3/8	0.2	1/4	0.2	1/4
17-20	0.2	3/8	0.2	3/8	0.2	3/8
21-24	0.2	1/2	0.2	1/2	0.2	1/2
25-28	0.2	3/4	0.2	1/2	0.2	3/4
29-32	0.2	1	0.2	1	0.2	1
33-35	0.2	1 1/2	0.2	1	0.2	1 1/2
36-39	0.2	2	0.2	1	0.2	2
40-42	0.2	2	0.2	2	0.2	2
43-45	0.2	3	0.2	2	0.2	3
46-49	0.2	5	0.	0	0.2	5
50-52	0.2	8	0.	0	0.	0
53-55	0.1	8	0.	0	0.	0
56-60	0.	8	0.	0	0.	0

1. Preliminary Study. The roentgenographic examination of the gastro-intestinal tract, using barium sulphate and water as the opaque medium, performed before beginning the propeptan treatment.
2. Pretreatment Study. The roentgenographic examin-

* The Propeptans used in this study were supplied by Delare Associates, Phila., Pa.

ation of the gastro-intestinal tract performed before the commencement of the propeptan therapy in which opaque medium contained barium, water and the food to which the patient was hypersensitive.

3. Post-treatment Study. The roentgenographic examination of the gastro-intestinal tract performed after the completion of the propeptan therapy in which the opaque medium was identical with that used in the pretreatment study.
4. Narrowing. Multiple areas of varying length of narrowing (below 1.5 cm.) in the caliber of the small bowel.
5. Segmentation. Loss of continuity of the barium column due to breaking up into small boluses, separated by areas of narrowing.
6. Scattering. Quantities of barium of varying size retained in the ileum after the tail of the barium column had passed.
7. Transit Time. Time after swallowing required for the barium to reach the cecum.

Group A. (Gastro-Intestinal Food Hypersensitive Patients without Psychiatric Disturbances). In all seven patients in this group, the preliminary roentgenographic examination showed no abnormalities while the pretreatment examination showed abnormalities in all instances. The post-treatment examination gave normal results, or almost normal ones, in all patients.

In the two cases in which the mucosal folds of the stomach were wide and edematous in the pretreatment study (cases 1 and 6) the post-treatment stomach pattern was normal. In five instances the opaque medium had reached the cecum in one hour in the pretreatment study (cases 1, 2, 3 and 6). (Some of the patients had more than one allergenic study when sensitivity to more than one allergen was present). In the post-treatment examination, the barium had reached the cecum at the end of one hour in two of these instances, both being in the same patient (case 1). In one case, however, (case 4) the head of the barium column had reached the cecum at the end of one hour in the post-treatment examination, while it had only reached the terminal ileum in the pretreatment study.

As previously reported (1e), the most striking changes in the intestinal tract in cases of gastro-intestinal food hypersensitivity occur in the lower portion of the small bowel. Numerous areas of narrowing were noted in all of the pretreatment studies, while minimal areas of narrowing were present in three of the post-treatment studies (cases 1, 2 and 6). Segmentation occurred in all but one instance in the pretreatment examinations (case 3) but was absent after treatment in all studies. Scattering was present in all but one of the pretreatment studies (case 2), but was absent in all the post-treatment studies.

Six hour gastric retention was present in three instances before treatment (cases 1, 5 and 7) but had disappeared in all but one case after treatment (case 1).

None of the patients were discomforted by the preliminary barium-water study, while all but one (case 6) complained of severe distress during or shortly after the pretreatment study. The symptoms varied from epigastric distress and nausea to severe abdominal pain and diarrhea. One patient (case 3), in addition to having gastro-intestinal manifestations, had an asthmatic attack. None complained of any distress during or after the post-treatment study, although the allergen was present in the contrast medium.

The information gathered from the study of group A is listed in Table II.

The following histories are representative of the patients investigated.

Case 1. I. H., a 35-year-old white woman was admitted to the Medical Ward on 7 May, 1947, complaining of nausea, vomiting and headache following the ingestion of certain foods. She had been extremely sensitive to egg and pork since early childhood. As long as she can remember, her symptoms began with uneasiness one to two hours after the ingestion of the offending food with pain, nausea and vomiting following and becoming more severe 12 to 36 hours later. On admission the patient had been vomiting almost constantly for two weeks and had lost 9.1 Kg. (20 lbs.) during this time.

Her mother suffered from migraine, aggravated by milk and the patient had cyclic vomiting and diarrhea in childhood, aggravated by egg and pork. There were occasional migraine-like headaches since the menarche at age 13 and frequent aphthae, coating of the tongue and flatulence.

At the time of admission, the patient was a fairly well-developed and well-nourished but severely dehydrated white woman without other abnormal findings on physical examination, except for slight abdominal tenderness.

Small Bowel Studies: The preliminary barium-water study showed nothing abnormal. The barium-egg study, performed before propeptan therapy was significantly abnormal. The mucosa of the stomach was edematous and showed widening of the rugal folds. At one hour, the head of the barium column was in the sigmoid colon and at six hours, in the rectum. The upper small bowel pattern was normal but there was narrowing, segmentation and scattering of the barium in the ileum. The stomach was empty at the end of three hours. The transit time was two hours. In the pretreatment barium-pork test, the mucosal pattern of the stomach was normal. At one hour, the head of the barium column was in the cecum; at six hours, in the ascending colon. The upper small bowel pattern was normal but there was narrowing, segmentation and scattering of the barium in the ileum. There was gastric retention at the end of six hours. The transit time was one hour. During both the barium-egg and barium-pork pretreatment studies, the patient developed severe abdominal cramps.

The patient received propeptan therapy for six weeks, using type-specific egg and pork digests simultaneously. At the end of 10 days of treatment, the patient had only slight symptoms, and, after three weeks was symptom free. She has remained symptom free, ingesting average normal quantities of egg and pork until the present time, a period of seven months.

The barium-egg test performed after the completion of the propeptan treatment showed a normal mucosal pattern of the stomach. At one hour, the head of the barium column was in the proximal portion of the ascending colon; at six hours, in the ascending colon. There was no evidence of narrowing, segmentation or scattering in the small bowel. The stomach was empty at the end of three hours. The transit time was one

TABLE II

Results of Propeptan Therapy: Roentgenographic Findings in Food-Hypersensitive Persons without Psychiatric Disturbances (Group A)

	Case 1					Case 2					Case 3	
Status of Patient	Untreated			Treated		Untreated			Treated		Untreated	
Contrast Medium (Barium and:—)	Water	Egg	Pork	Egg	Pork	Water	Milk	Egg	Milk	Egg	Water	Corn
Mucosal Pattern of Stomach	N	Wide Edema	N	N	N	N	N	N	N	N	N	N
Head of Barium Column at 1 Hr.	Jejunum	Sigmoid Colon	Cecum	Asc. Colon	Cecum	Jejunum	Jejunum	Asc. Colon	Upper Ileum	Ileum	Ileum	Cecum
Upper Small Bowel Pattern	N	N	N	N	N	N	N	N	N	N	N	N
Lower Small Bowel Pattern:—												
Narrowing	-	/	/	-	†	-	/	/	-	†	-	/
Segmentation	-	/	/	-	-	-	/	/	-	-	-	-
Scattering	-	/	/	-	-	-	-	/	-	-	-	/
Transit Time (hrs.)	3	2	1	1	1	3	2	1	2	2	2	1
Emptying Time of Stomach (hrs.)	3/	3/	6/	3	6/	3	3	3	2	3	2	3
Head of Barium Column at 6 Hrs.	Asc. Colon	Rectum	Asc. Colon	Asc. Colon	Asc. Colon	Trans. Colon	Trans. Colon	Desc. Colon	Trans. Colon	Desc. Colon	Asc. Colon	Sigmoid Colon
Patient's Symptoms	-	Severe Abd. Pain	Severe Abd. Pain			-	Epig. Pain	Epig. Pain	-	-	-	Acute Asthma
Clin. Improvement After Treatment	-	-	-	Excel-lent	Excel-lent	-	-	-	Excel-lent	Excel-lent	-	-

N equals Normal / equals Present - equals Absent † equals Minimal

TABLE II

Results of Propeptan Therapy: Roentgenographic Findings in Food-Hypersensitive Persons without Psychiatric Disturbances (Group A)

Case 3 (contin.)				Case 4				Case 5		Case 6		Case 7		
Untreated		Treated		Untreated		Treated		Untreated	Treated	Untreated	Treated	Untreated		Treated
Milk	Corn	Milk	Water	Milk	Milk	Water	Egg	Egg	Water	Milk	Milk	Water	Milk	Milk
N	N	N	N	N	N	N	N	N	N	Wide Edema	N	N	N	N
Jejunum	Ileum	Jejunum	Ileum	Term. Ileum	Cecum	Ileum	Ileum	Ileum	Ileum	Asc. Colon	Ileum	Ileum	Jejunum	Ileum
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
/	-	-	-	/	-	-	/	-	-	/	†	-	/	-
/	-	-	-	/	-	-	/	-	-	/	-	-	/	-
/	-	-	-	/	-	-	/	-	-	/	-	-	/	-
6	2	3	6	3	1	3	6/	3	2	1	2	3	6	3
3/	2	2	6	3/	3/	2/	6/	2	2	3	3	3	6/	3
Cecum	Asc. Colon	Asc. Colon	Term. Ileum	Asc. Colon	Cecum	Asc. Colon	Ileum	Trans. Colon	Asc. Colon	Trans. Colon	Asc. Colon	Term. Ileum	Cecum	Term. Ileum
Vague Epig. Pain	-	-	-	Vague Epig. Pain	-	-	Nausea Epig. Pain	-	-	-	-	-	Nausea Epig. Pain	-
-	Excel-lent	Excel-lent	-	-	Excel-lent	-	-	Excel-lent	-	-	Excel-lent	-	-	Excel-lent

N equals Normal / equals Present - equals Absent † equals Minimal

hour. The patient experienced no symptoms during the study. In the post-treatment barium-pork test, the mucosal pattern of the stomach was normal. The head of the barium column was in the cecum at the end of one hour; in the ascending colon at six hours. There was no segmentation or scattering in the lower small bowel but minimal narrowing was present. Six hour gastric retention was still present. The transit time was three hours. No symptoms occurred during the test.

The roentgenographic findings are shown in Fig. 1 and tabulated in Table II.

Case 6. M. S., a 47-year-old white housewife, was admitted to the Medical Ward on 10 June, 1947 for evaluation of her cardiac status. Shortly before admission, she developed an acute attack of nausea and vomiting associated with loss of hearing, which persisted for two days. Questioning revealed that she had had similar episodes for "several" years. For the six months preceding admission, there had been periods of gnawing epigastric distress aggravated by cream or ice cream. Her appetite was good and there had been no weight loss. There was no family history of allergic diseases. She had had cyclic vomiting in childhood and one attack of eczema relieved by "local medication." Since childhood, she has had migraine-type headaches, occurring once to twice each year. There has been marked constipation, frequent stomatitis, aphthae and edema of the tongue following the ingestion of ice cream or cream. The dietary habits are normal. There is no other food hypersensitivity.

She is moderately well-developed, poorly nourished white woman in no immediate distress. Except for a functional systolic mitral murmur, no abnormalities were noted on physical examination.

Small Bowel Studies: The preliminary barium-water study was normal. In the pre-treatment barium-milk study, there was widening and edema of the mucosal folds of the stomach. At one hour, the head of the barium column was in the ascending colon; at six hours, in the transverse colon. The upper small bowel pattern was normal. There was narrowing, segmentation and scattering in the lower small bowel. The stomach was empty at the end of three hours. The transit time was one hour.

The patient received propeptan therapy for five weeks, using type-specific milk digest. At the end of three weeks the patient was symptom free and has remained so, ingesting average quantities of milk, until the present time, a period of six months.

The barium-milk test, performed after the completion of the propeptan therapy, showed a normal pattern of the stomach mucosa. At one hour, the head of the barium column was in the ileum; at six hours, in the ascending colon. The entire small bowel pattern was normal with the exception of minimal narrowing in the lower portion. The stomach was empty at the end of three hours. The transit time was two hours. The patient had no symptoms during either examination.

The roentgenographic findings are shown in Fig. 2 and tabulated in Table II.

Group B. (Gastro-Intestinal Food Hypersensitive Patients with Psychiatric Disturbances). The preliminary barium-water study was normal in the three patients in this group. The mucosal pattern of the stomach, the position of the head of the barium column at the end of one and six hours, the upper small bowel pattern, the transit time and the emptying time of the stomach were all within normal limits in both the pretreatment and post-treatment studies. Narrowing and segmenation were present in the lower portion of the small bowel in all the pretreatment studies. Scattering was absent in one case (case 10). With the exception of minimal scattering in one instance (case 9) none of these changes were noted in the lower small bowel pattern in the post-treatment studies. All experienced clinical symptoms during or shortly after the pretreatment study; none during or shortly after the post-treatment study. However, as will be discussed later, the amelioration of symptoms in this group was only temporary.

The information gathered from the study of group B is listed in Table III.

DISCUSSION

Until the introduction of type-specific propeptan therapy, the treatment of gastro-intestinal food-hypersensitivity had been both difficult and prolonged and the results had not been entirely satisfactory. The three most commonly used methods of treatment have been, according to Vaughan (20), (1) elimination, (2) desensitization and (3) skeptophylactic desensitization.

1. Elimination. This is the oldest and most reliable of all measures. The offending food and all its products are eliminated from the diet for prolonged periods; sometimes for the entire life of the patient. This method is useful if the sensitivity is due to some non-essential constituent of the diet, but is both impractical and difficult to enforce if there is sensitivity to a commonly used, highly nutritious food, such as milk or egg.

2. Desensitization consists of administering slowly increasing quantities of the food to which the patient is hypersensitive. This method is theoretically possible, but practically it is time consuming, often unsatisfactory and not without danger. Very small quantities of the food may produce constitutional reactions and death from anaphylactic shock has been reported (21).

3. Skeptophylactic Desensitization was first described by Besredka (8b). Minute amounts of all foods to be served at the meal are given 45 minutes before the meal for several months. This procedure frequently produces good results but is irksome due to the length of time required.

The propeptan therapy of food-hypersensitivity (Luithlen (16), E. Urbach (2b, c) has been used in Europe and South America (17) for many years with excellent clinical results, but has not been given any extensive clinical trial in the United States. The procedure is simple, the diet is adequate from the onset of treatment and permanent deallergization is apparently produced.

According to E. Urbach and associates (22), propeptans are preparations resulting from digestion of individual proteins by hydrochloric acid, pepsin and trypsin. They are composed of proteoses, peptones, subpeptones, simple peptides and amino acids in definite proportions but contain no undigested protein as do commercial "peptones." They are type specific and will protect animals sensitized by either the intravenous, subcutaneous or oral routes, against otherwise certain death in anaphylactic shock.

The mechanism underlying the beneficial action of the food digests (propeptans) has not been entirely

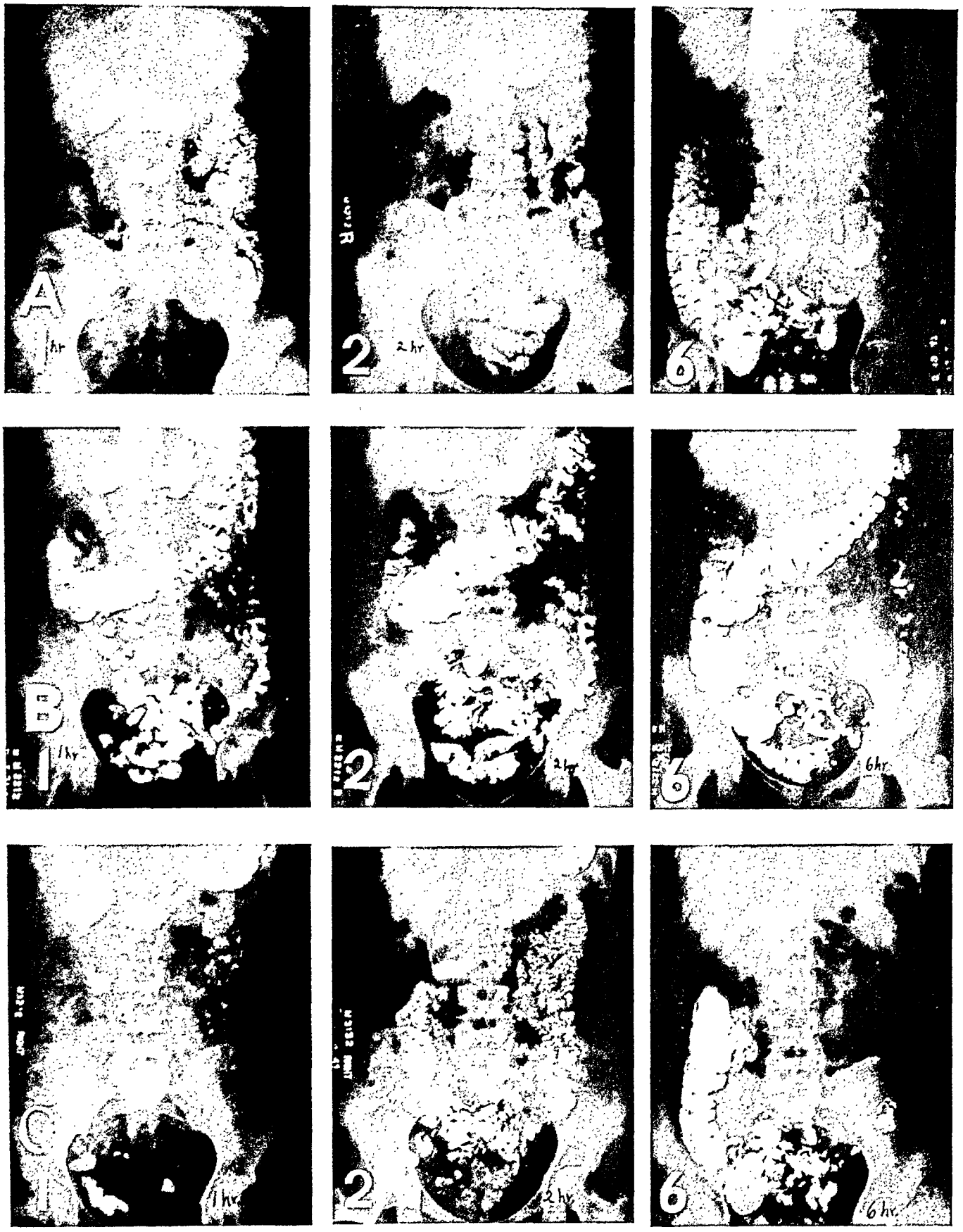


Fig. 1A (case 1) — Roentgenogams taken at 1, 2 and 6 hours of a patient with gastro-intestinal hypersensitivity to egg and pork.

Row A. — Preliminary barium-water study showing no abnormalities.

Row B. — Pretreatment barium-water-egg study showing hypermotility with narrowing, segmentation and scattering in the ileum. Row C. — Post-treatment barium-water egg study showing slight hypermotility.

explained. E. Urbach and Gottlieb (23) offered a working hypothesis to explain the method by which skeptophylactic treatment by the oral route renders tissue antibodies incapable of reacting with the antigen, at least in the major shock organs. They suggested that appropriate administration of small amounts of antigen elicit so-called micro-shocks (antigen-antibody reactions) which temporarily bind the tissue antibodies. Newly formed antibodies are, in turn, satiated by the antigen being slowly absorbed from the gastro-intestinal tract. They are of the opinion that these micro-shocks not only bind the tissue antibodies but also cause an exhaustion of the antibody forming organs, resulting eventually in the arrest of antibody production and deallergization. This deallergization is, at first, temporary but becomes apparently permanent after several weeks of continuous oral treatment. By using food digests (propeptans) which retain the specificity of the undigested protein but are much less antigenic, the systemic reactions accompanying the micro-shocks are either completely eliminated or greatly minimized.

In our small group of patients (group A) who had both clinical and roentgenographic evidence of food-hypersensitivity, but had no psychiatric disturbances, uniformly excellent results were obtained using propeptan therapy. All felt considerably improved after the first week of treatment and were practically symptom-free at the end of the second week. Insufficient time has elapsed to determine the permanence of the deallergization but to date (i. e. four to seven months) all are symptom free. Aside from the clinical improvement, which is a subjective method of evaluation, the objective roentgenographic studies of the gastro-intestinal tract, administering the allergen in the contrast medium, were either completely normal or greatly improved at the completion of the treatment as in contrast to the abnormal findings obtained before the treatment (Table II).

The three patients with both food-hypersensitivity

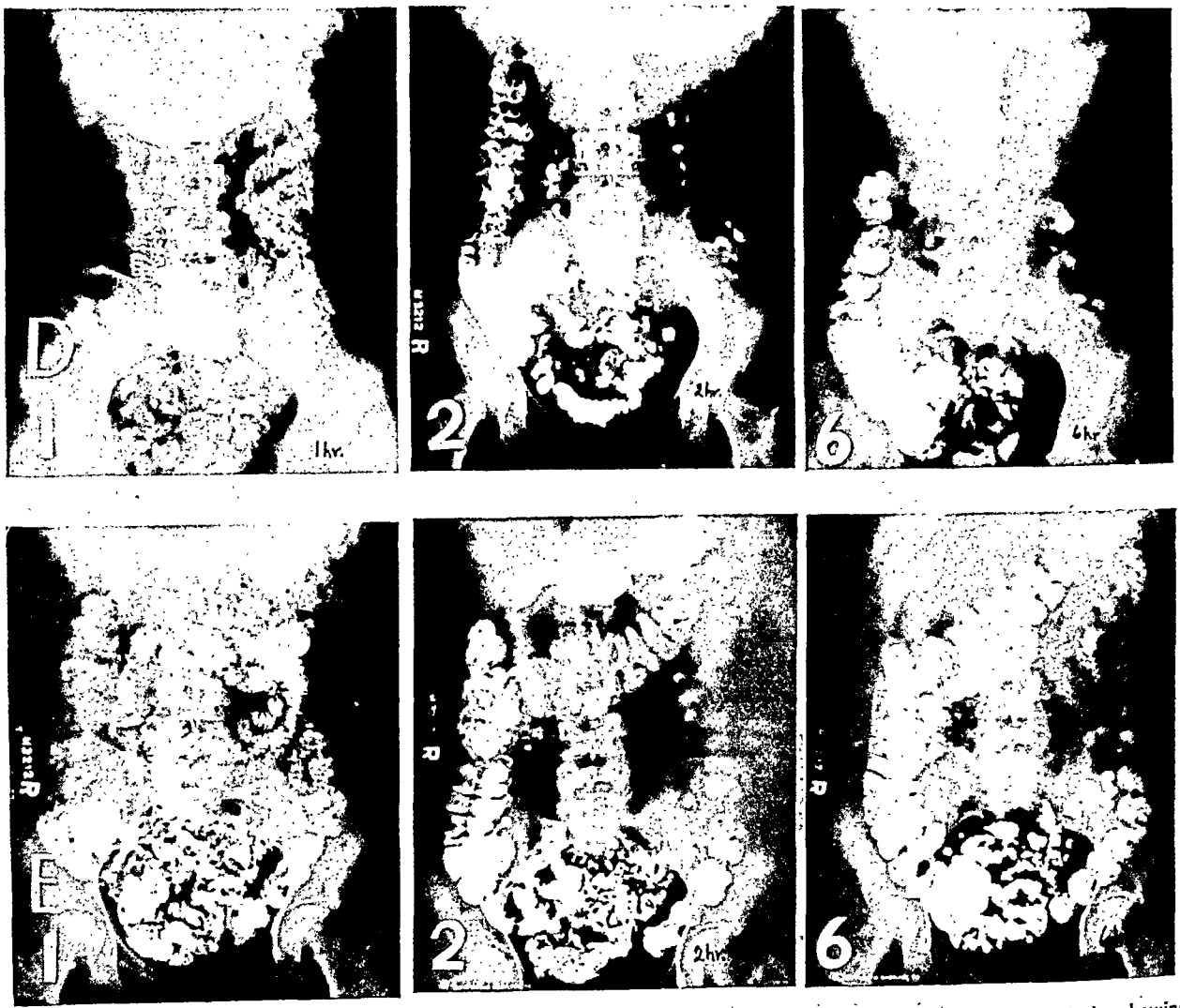


Fig. 1B (case 1) — Same patient as Fig. 1A. Row D. — Pretreatment barium-water-pork study showing hypermotility, narrowing, segmentation and scattering in the ileum and 6 hour gastric retention. Row E. — Post-treatment barium-water-pork study showing minimal narrowing in the ileum and 6 hour gastric retention.

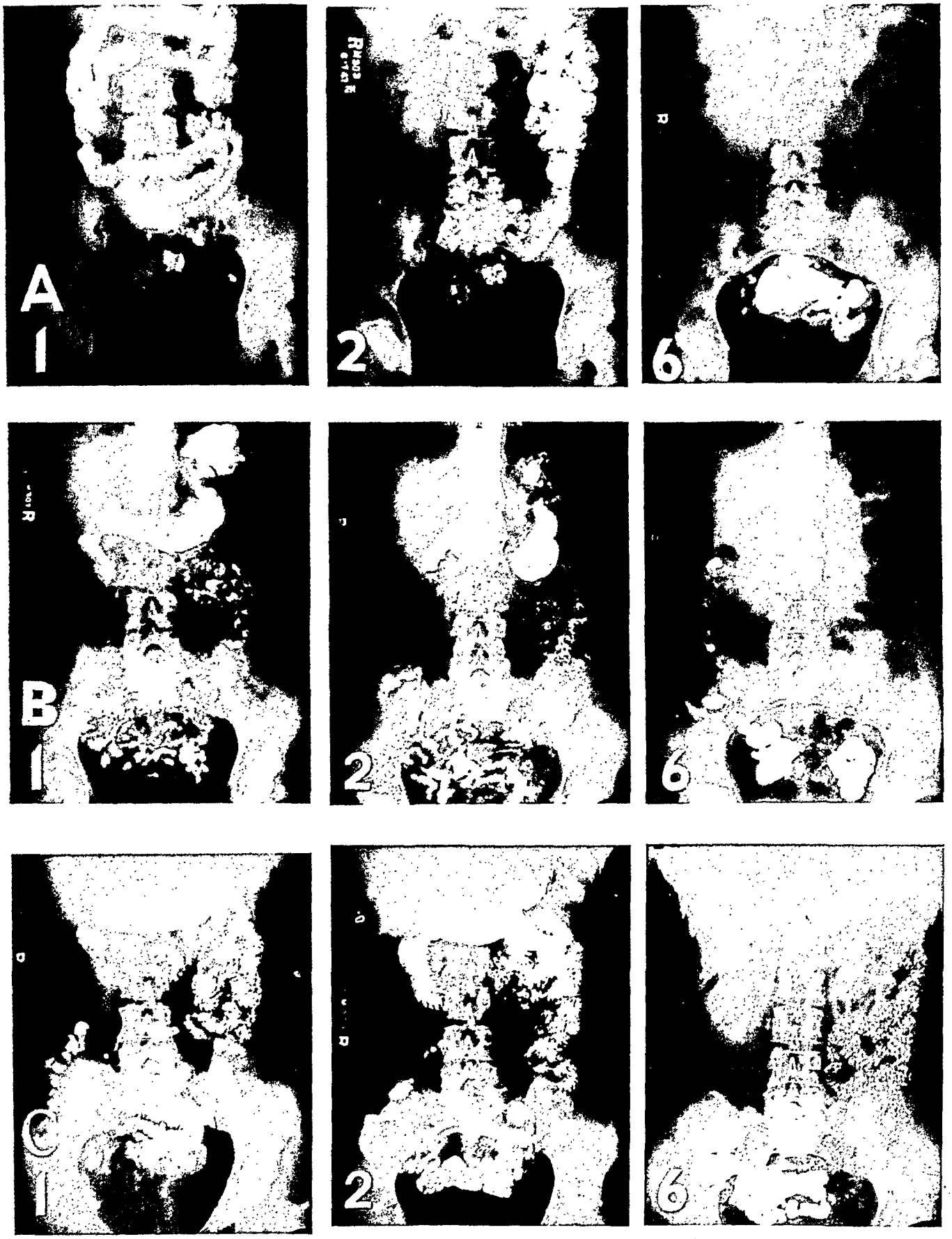


Fig. 2. (case 6) — Roentgenograms taken at 1, 2 and 6 hours of a patient with gastro-intestinal hypersensitivity to milk.
Row A. — Preliminary barium-water study showing no abnormalities.
Row B. — Pretreatment barium-water-milk study showing widening of the mucosal folds of the stomach, hypermotility with narrowing, segmentation and scattering in the ileum.
Row C. — Post-treatment barium-water-milk study showing minimal narrowing in the ileum.

TABLE III.

Results of Propeptan Therapy: Roentgenographic Findings in Food-Hypersensitive Persons with Psychiatric Disturbances (Group B)

	Case 8			Case 9			Case 10		
Psychiatric Disturbances	Anxiety-Tension State, Severe			Anxiety-Tension State, Severe			Hypochondriasis Severe		
Status of Patient	Untreated		Treated	Untreated		Treated	Untreated		Treated
Contrast Medium (Barium and:—)	Water	Milk	Milk	Water	Milk	Milk	Water	Milk	Milk
Mucosal Pattern of Stomach	N	N	N	N	N	N	N	N	N
Head of Barium Column at 1 Hr.	Ileum	Ileum	Ileum	Jejunum	Ileum	Upper Ileum	Ileum	Ileum	Ileum
Upper Small Bowel Pattern	N	N	N	N	N	N	N	N	N
Lower Small Bowel Pattern:—									
Narrowing	-	/	-	-	/	-	-	/	-
Segmentation	-	/	-	-	/	-	-	/	-
Scattering	-	/	-	-	/	±	-	-	-
Transit Time (hrs.)	2	3	2	3	2	6	3	6	4
Emptying Time of Stomach (hrs.)	3	3	3	1	3	1	1	3	2
Head of Barium Column at 6 Hrs.	Cecum	Cecum	Cecum	Asc. Colon	Rectum	Rectum	Trans. Colon	Trans. Colon	Trans. Colon
Patient's Symptoms	-	Abd. Pain	-	-	Diarrhea	-	-	Abd. Pain	-
Clin. Improvement After Treatment	-	-	Temporary	-	-	Temporary	-	-	Doubtful

N equals Normal / equals Present - equals Absent ± equals Minimal

and severe psychiatric disturbances (group B) responded satisfactorily to the propeptan therapy for the first three weeks. However, following this initial improvement, symptoms recurred and have persisted although the therapy was continued. The roentgenographic examinations of the gastro-intestinal tract, performed after the completion of the treatment, mixing the allergen in the contrast medium, were normal in all three instances, contrasted with the abormal pretreatment findings (Table III). It would thus appear that the actual food-hypersensitivity of these patients was relieved and that the recurrence of symptoms was due to psychiatric factors. This opinion is in agreement with the findings of Bauer and others (18).

In the use of the propeptan method of treatment of food-hypersensitivity there are certain facts which must be constantly borne in mind if good results are to be obtained.

1. If the food is not of protein origin (i. e. fats, carbohydrates, acids and salts) the procedure is of no value (24).

2. Propeptan therapy must be accurately administered. The capsule must be given exactly 45 minutes before meals. No food should be eaten between meals and careful attention should be given to the basic constituents of prepared foods. (e. g. milk and egg in cake).

3. Unusually severe hypersensitivity requires several times the usual propeptan dosage and a slower rate of increase in the quantity of the food to which the patient is hypersensitive.

4. The ingestion of very large quantities of the food to which the patient was previously sensitive may result in a recurrence of the sensitivity after the completion of the treatment.

5. Factors which may predispose to gastro-intestinal food-hypersensitivity should be eliminated. Among these factors are excessive food intake, parasitic infections, hepatic disease, physiological abnormalities and pathological states of the gastro-intestinal tract, endocrine dysfunctions, infectious diseases and psychic factors (19b).

SUMMARY

1. The results obtained in the treatment of 10 patients suffering from gastro-intestinal food hypersensitivity, using type-specific food digests (propeptans) are described.

2. Excellent clinical improvement occurred in seven

of the 10 patients. The three patients who obtained only temporary clinical improvement had severe psychiatric disturbances.

3. Roentgenographic abnormalities of the gastro-intestinal tract, present before the institution of the treatment, completely or almost completely disappeared in all patients following the completion of the treatment.

4. The method of treatment, the possible mechanism of action and the sources of error are discussed.

5. The promising results of this small series warrants further study and treatment of other patients who have gastro-intestinal sensitivity to food.

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The Presence of an Anti-Rh Agglutinin in Commercially Available Medicinal Hog Gastric Mucin

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THE SO-CALLED RHESUS (Rh) factor agglutinins have been of concern chiefly to obstetricians and to transfusionists. A gastro-intestinal implication arose with the demonstration of the presence of an Rh antibody in the milk of sensitized mothers (1). It was implied that this antibody could be absorbed by the nursling with possible further passive sensitization of the latter. On this basis, nursing of erythroblastotic infants by their own mothers was interdicted. If the interdiction is proper it must be assumed that this Rh antibody withstands gastric and intestinal digestion.

Of theoretic interest in connection with the possible enteral absorption of Rh antibody is the fact that we have demonstrated in ordinary commercial hog gastric mucin used for the treatment of peptic ulcer, an Rh pseudoagglutinin which is similar to that present in the milk of Rh sensitized mothers in that the former, likewise is of the "blocking" type and, by virtue of its method of preparation must also resist at least the gastric phase of digestion. Though we have observed no instance of passive Rh sensitization through the administration of hog mucin to humans, the same implications would appear to be attached to this antibody as to that ingested along with the milk of sensitized mothers.

We were led to an examination of hog mucin for Rh pseudoagglutinin through its previous demonstration in hog parotid mucin. The latter, at one time was incorporated in the commercial therapeutic mucin (2). Pig parotid, in turn, had been examined along with other glycoprotein-rich tissue preparations after it had been demonstrated that there was a considerable concentration of Rh "blocking antibody" in the glycoprotein-containing IV-6 fraction from human plasma of presumably normal donor pools (3). It may be remarked in passing that the presence of a "blocking antibody" or pseudoagglutinin which shows a significant degree of selectivity for Rh positive human erythrocytes, is unique neither to the pig nor to the human but has been found in a variety of animal and even in plant materials (4). The immunologic specificity of the Rh factor thus remains an open question of the definition of "specificity." This question, while it merits mention, is not germane to this report which deals with the method of demonstration and characterization of an Rh "antibody" in hog gastric mucin.

EXPERIMENTAL

The high viscosity of concentrated crude mucin solutions impedes the agglomeration of erythocytes upon which demonstrable agglutination depends. Although it is possible to demonstrate agglutination of Rh positive human erythrocytes by a 2% solution of crude mucin in physiologic saline, for definitive studies the pseudoagglutinin was concentrated and freed from viscid mucin. This was accomplished by dissolving three grams of crude mucin in 100 cc. of 0.9% NaCl. solution in a 200 cc. beaker and adding glacial acetic acid, dropwise, until the pH (as measured by the glass electrode) was 4.5. An equal volume of dioxane was then added to fill the beaker which was covered with a watch glass and allowed to stand overnight in the refrigerator. A creamy-yellow precipitate had formed by the next morning and was found adhering to the bottom of the beaker. The supernatent fluid was decanted and discarded and the precipitate dissolved by the addition of 20 cc. of 0.9% NaCl solution to the precipitate. A turbid solution results which was clarified by the dropwise addition of 10% Na_2CO_3 solution to a final Ph of 6.8.*

Amenability of human erythrocytes to agglutination by mucin extract was determined on the basis of the so-called "conglutination" or slide test. Human blood samples were obtained in citrate-Vacutainers (5) and the Rh and hemagglutination category determined by the use of standard human typing antiserums. A drop of the citrated blood was placed within a paraffined ring on a glass slide and a drop of the hog mucin extract added. (In some instances, the latter was made up in 10% modified human globin (6) as a rouleaux facilitator since the conglutination test appears to be contingent upon the formation of rouleaux). The slide with the reagent-

* The investigative work upon which this report is based was conducted at Halloran General Hospital, Staten Island, N. Y. and the Veterans Administration Hospital, Batavia, N. Y.

* On continuous standing in the ice box for two or three weeks, the latter solution deposits the traces of viscid mucin that remain, without loss of agglutinating effect on Rh positive human erythrocytes.

blood mixture was placed upon a ground glass illuminator and the degree of agglutination read macroscopically at the end of five minutes and at the end of twenty minutes.

Where agglutination occurred within five minutes of mixing, the sample was recorded as positive with the rough quantitative designation of one, two, three or four plus. Where agglutination was negative at the end of five minutes but appeared before twenty minutes had elapsed, the result was designated as "doubtful." Samples showing no agglutination (microscopically confirmed) at the end of twenty minutes, were called "negative."

"Blocking" effect was tested by suspending washed Rh positive erythrocytes in varying concentrations crude hog gastric mucin in physiologic saline, centrifuging, discarding the supernatent and resuspending in standard Rh_0 human antiserum. The results were read after recentrifuging, by the original Wiener-Landsteiner technique as applied to blocking antibody demonstration by Potter *(7)*.

RESULTS

Table I gives the comparative results on twenty blood samples with representative distribution. It indicates the strong parallelism between the human and the porcine agglutinin. The results seem to be contingent upon the Rh status of the tested erythrocytes and to be independent of the classic blood groupings except for traces of an anti-A factor. The latter gives a microscopically demonstrable pseudoagglutination in some A_1 blood samples.

Weak agglutination within the five minute period on Rh_0 negative blood samples was noticed only where the latter were rh′ and/or rh″ positive. We have encountered no instance of agglutination in Rh_0 rh′ rh″ negative erythrocytes.

The blocking antibody titer of several lots of hog gastric mucin in 2% solution was 1:7.

DISCUSSION

The presence of an antibody with the definitive characteristics of an anti-Rh substance in hog gastric mucin raises several points of discussion all of which while admittedly speculative, are of potential importance. First, does the therapeutic administration of hog gastric mucin produce passive Rh sensitization in the recipient and possible accelerated hemoclasis in the same manner as the rhesus factor in ingested human milk is supposed to operate in an Rh positive infant? Or, second and contrawise, would the ingestion of an absorbable blocking antibody act to prevent active sensitization should an Rh negative

TABLE I

Comparative Agglutination of Human Erythrocytes by Standard Human Antiserum (Rho) and Hog Mucin Extract

Sample	Aglutination Reaction Human Antiserum	Hog Mucin	Blood Type	Remarks
An. B.	++++	+++	A pos.	
Ba.	+	doubtful	A neg.	rh′ pos.
Br.	+++	+++	B pos.	
Wa.	++	++++	O pos.	
Ka.	+++	++++	?	
Bay.	++	++	A pos.	old blood
Al.	+	doubtful	A pos.	old blood
Go.	++	negative	A neg.	rh″ pos.
Ro.	++++	+++	O pos.	
Rot.	negative	negative	O neg.	rh′ rh″ unknown
St.	negative	++	A pos.	transfusion reaction-post-gastrectomy
Ga.	+++	++++	?	
Le	+++	+	A pos.	
Ant.	+++	+++		
O'B.	++++	++	O pos.	
Mai.	negative	doubtful	AB neg.	rh′ rh″ unknown
Man.	+++	++++	A pos.	transfusion reaction-post-gastrectomy
Re.	negative	negative	B neg.	rh′ rh″ negative
Fo.	doubtful	+++	O pos.	
Li.	negative	negative	O neg.	rh′ rh″ negative

ulcer patient on mucin therapy receive inadvertent Rh positive transfusions? Both these possibilities are so remote that they can only be answered by continued clinical observation.

Thirdly, there is some suggestion that a blocking antibody may be of therapeutic utility in the active treatment of some cases of erythroblastosis. It is not inconceivable that porcine material, with its inexpensiveness and plentitude could be the starting source in the development of such a therapeutic product.

The fourth point is the possible necessity for the rigid examination of the current genetic theories to account for the natural occurrence of a "rhesus" factor in porcine materials. Such an exploration may be belated. The continued growth and arborization of Rh subtype from type has become somewhat confusing to the physician who is not a trained geneticist. We are still faced by the fact that Rh "agglutination" differs radically in its physical characteristics from specific (i. e. A and B) hemagglutination, the former being more like the pseudoagglutination produced by alkali or other lipolytic hemolysins (8). On the other hand, that there is a demonstrable difference between "Rh positive" and "Rh negative" human erythrocytes, inherent in the latter, is undeniable. The difference even exists toward hog gastric mucin extract.

SUMMARY

Commercial gastric mucin designed for the treatment of human gastric ulcer contains an Rh antibody of the blocking type. The significance of the presence of this antibody in a porcine product is unknown.

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Dextrose, Insulin and Epinephrine Tolerance Tests in Cirrhosis of the Liver.

By

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A VARIETY OF TESTS have been designed to detect disturbances of carbohydrate metabolism in hepatic disease. Some, such as the levulose and galactose tolerance tests, have shown a fair degree of correlation with the amount of pathological change encountered. The dextrose tolerance test, however, has often failed to indicate existing liver damage, and this lack of sensitivity might be expected in the closely related insulin and epinephrine tolerance tests as well.

In order to determine the comparative validity of the dextrose, insulin and epinephrine tolerance tests and the extent to which they exhibit parallel results, all three were performed in a series of patients with cirrhosis of the liver.

Blood serum inorganic phosphate values were determined together with blood glucose levels, since concomitant changes are usually observed during the active metabolic processes of which these are the two most widely applied indexes.

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MATERIAL AND METHODS

Seventeen cases were studied, comprising 15 of Laennec's cirrhosis, one of biliary cirrhosis and one of post-necrotic cirrhosis. All presented clinical and laboratory evidence of the disease, and in 13 the diagnosis was confirmed by biopsy, autopsy or both. The dextrose tolerance test was performed in each, but all three tests were completed in only 14.

Patients were on a nutritious, high protein diet, containing approximately 365 grams of carbohydrate (1) for a period of at least one week prior to the dextrose study, further standardization of food intake being held unnecessary (2). A similar interval was allowed between subsequent tests, the insulin tolerance usually being determined second.

The *intravenous* dextrose tolerance test was employed to provide a uniform load by eliminating the factor of absorption (3), an especially significant variable in patients with portal hypertension and/or ascites. Moreover, the liver apparently metabolizes parenterally administered sugar much as it does that ingested (4, 5, 6). The dose was 25 grams (50 cc. of a 50% solution) in each instance, the factor of body weight, apparently important with smaller quantities (7), being reported as without influence at the higher level (8, 9). The solution was injected at

maximum possible speed, usually through a 20 gage needle, since it has been shown that variations of two to four minutes in the time of injection have no effect on the subsequent blood sugar curves (9). Blood samples were obtained in the fasting state preceding, and at 1/2, 1 and 2 hour intervals following injection of each test substance. Samples were analyzed for blood sugar by the modified method of Benedict (10) and for serum inorganic phosphate by the method of Fiske and Subbarow (11).

In the insulin tolerance test a standard test dose of 10 units intravenously was arbitrarily employed at first. Later, because of a severe reaction in one patient, the more widely accepted dose of 0.1 unit per kilogram of body weight (12) was adopted.

The epinephrine tolerance test consisted of the intramuscular injection of 0.6 cc. of a 1:1000 solution (0.6 mgm.) the dose reported as most suitable for determining this response (12, 13).

RESULTS

Results are recorded in Table I.

Dextrose Tolerance Test: Usually the blood sugar level two hours after the intravenous injection of a stated quantity of glucose should be at or below the fasting figure (7, 8); the height of the curve is thought to be without significance (40), especially since it evidently reflects the rate of diffusion as well as of the metabolism of the sugar (14). In this study a two hour level that exceeds the fasting figure by more than five mgm. per cent is regarded as abnormal ("diminished response") and one that falls to 15

TABLE I

Patient	Sex	Age	Diagnosis	Test	Substance	Blood Level MGM % Fast	1/2 Hr.	1 Hr.	2 Hr.	Per Cent Change
				D. T. T.	Sug.	93	186	132	88	+50
					In. P.	1.9	1.9	1.9	2.1	+11
1. T. S.	M	71	Laennec's	I. T. T.	Sug.	96	56	59	91	—42
					In. P.	2.6	2.1	1.7	1.9	—35
				E. T. T.	Sug.	85	103	116	104	+36
					In. P.	2.7	2.1	2.6	2.6	—22
				D. T. T.	Sug.	64	150	82	70	+134
					In. P.	3.8	3.7	3.5	3.5	—8
2. A. H.	F	56	Laennec's	I. T. T.	Sug.	80	35	56	76	—56
					In. P.	3.7	2.8	2.8	3.4	—24
				E. T. T.	Sug.	80	103	112	84	+40
					In. P.	3.4	3.3	3.4	3.4	—3
				D. T. T.	Sug.	89	152	136	86	+71
					In. P.	4.0	3.6	3.2	3.3	—20
3. C. J.	M	76	Laennec's	I. T. T.	Sug.	70	52	45	59	—36
					In. P.	2.5	2.0	2.2	2.4	—20
				E. T. T.	Sug.	83	97	95	76	+17
					In. P.	2.3	2.5	2.4	2.8	+9
				D. T. T.	Sug.	96	163	116	87	+79
					In. P.	4.9	4.1	4.8	4.7	—16
4. W. H.	M	46	Laennec's	I. T. T.	Sug.	84	40	52	82	—52
					In. P.	3.5	3.0	2.7	3.1	—23
				E. T. T.	Sug.	96	105	120	89	+25
					In. P.	3.7	3.5	4.0	3.7	—5
				D. T. T.	Sug.	78	159	111	91	+103
					In. P.	4.0	4.9	3.7	3.8	—8
5. V. O'D	M	43	Laennec's	I. T. T.	Sug.	95	51	53	70	—45
					In. P.	7.2	5.1	4.7	5.7	—35
				E. T. T.	Sug.	80	101	113	92	+40
					In. P.	4.0	3.6	3.8	3.9	—10
				D. T. T.	Sug.	82	138	115	78	+68
					In. P.	4.1	3.5	4.1	4.2	—15
6. J. H.	M	50	Laennec's	I. T. T.	Sug.	79	53	82	92	—33
					In. P.	3.2	2.8	2.4	2.8	—25
				E. T. T.	Sug.	91	99	116	116	+27
					In. P.	2.6	3.0	2.9	2.9	+15
				D. T. T.	Sug.	94	186	124	85	+102
					In. P.	2.8	2.3	2.7	2.4	—18
7. E. F.	F	75	Laennec's	I. T. T.	Sug.	99	43	31	—	—68
					In. P.	2.6	2.2	2.1	—	—19
				E. T. T.	Sug.	88	110	127	127	+45
					In. P.	3.1	3.3	2.9	3.1	—6
				D. T. T.	Sug.	78	124	107	63	+59
					In. P.	3.7	3.8	3.8	4.0	—8
8. T. C.	M	25	Laennec's	I. T. T.	Sug.	80	29	46	62	—64
					In. P.	4.0	3.0	3.6	3.0	—25
				E. T. T.	Sug.	70	96	98	78	+40
					In. P.	4.3	3.0	3.9	4.1	—30

TABLE I

Patient	Sex	Age	Diagnosis	Test	Substance	Blood Level MGM % Fast	1/2 Hr.	1 Hr.	2 Hr.	Per cent Change
				D. T. T.	Sug.	94	112	69	47	+33
					In. P.	5.0	4.4	3.7	4.6	+26
9. J. Mac L.	F	33	Laennec's	I. T. T.	Sug.	88	84	57	79	−61
					In. P.	5.8	5.8	4.4	6.6	−24
				E. T. T.	Sug.	73	93	122	121	+64
					In. P.	5.4	4.5	3.5	5.6	−22
				D. T. T.	Sug.	59	105	79	79	+32
					In. P.	2.6	2.4	2.5	2.2	−4
10. L. P.	M	21	Post-Nec.	I. T. T.	Sug.	75	79	52	46	−52
					In. P.	3.0	2.1	2.0	2.0	−33
				E. T. T.	Sug.	70	94	111	93	+46
					In. P.	2.9	3.0	3.0	3.4	+17
				D. T. T.	Sug.	104	150	116	162	+44
					In. P.	4.5	2.4	2.4	3.5	−29
11. C. G.	M	52	Laennec's	I. T. T.	Sug.	80	82	64	55	−31
					In. P.	2.4	2.7	2.2	2.4	−5
				E. T. T.	Sug.	92	100	110	112	+22
					In. P.	4.5	3.5	3.4	3.4	−13
				D. T. T.	Sug.	71	144	103	69	+103
					In. P.	4.9	4.6	4.6	4.6	−6
12. O. G.	F	49	Laennec's	I. T. T.	Sug.	58	31	33	44	−47
					In. P.	4.9	4.2	4.4	4.4	−14
				E. T. T.	Sug.	89	105	103	99	+18
					In. P.	4.5	4.5	4.4	4.5	−2
				D. T. T.	Sug.	99	154	130	97	+52
					In. P.	3.2	3.1	2.9	2.7	−16
13. K. M.	F	46	Laennec's	I. T. T.	Sug.	91	56	66	72	−23
					In. P.	3.2	2.4	2.9	2.6	−19
				E. T. T.	Sug.	65	97	94	81	+24
					In. P.	3.5	3.1	3.6	3.7	−11
				D. T. T.	Sug.	96	133	94	72	+33
					In. P.	7.9	6.3	5.7	5.7	−2
14. M. B.	M	54	Laennec's	I. T. T.	Sug.	67	52	54	57	−40
					In. P.	5.8	4.9	4.6	4.9	−21
				E. T. T.	Sug.	92	120	124	99	−36
					In. P.	5.9	3.7	3.4	3.4	−12
15. *E. B.	M	46	Laennec's	D. T. T.	Sug.	71	178	142	94	+151
					In. P.	3.5	3.2	3.2	3.2	−9
16. M. S.	F	59	Biliary	D. T. T.	Sug.	84	144	92	64	−74
					In. P.	2.6	2.3	2.3	2.5	−12
17. J. C.	M	76	Laennec's	D. T. T.	Sug.	88	165	139	120	+88
					In. P.	2.7	2.7	2.5	2.6	−19

* Poor food intake prior to test.

per cent or more below the fasting determination is classified as an "exaggerated response." This interpretation is purely arbitrary, particularly since curves reaching to 20 to 30 per cent below preinjection levels may sometimes be noted in the absence of obvious disease (3). Of 17 patients 12 showed a normal dextrose tolerance curve, three a diminished (pseudodiabetic) and two an exaggerated response.

Insulin Tolerance Test: These curves are likewise classified as normal, diminished, or exaggerated responses, with a maximum fall of 40 to 60 per cent below the fasting blood sugar level being regarded as the normal range (10 per cent on either side of the usually accepted figure of 50 per cent (12). Of the 14 patients in whom this test was performed six showed figures within these limits, four exhibited an exaggerated and four a diminished response.

Sensitivity to insulin seemed independent of the dose administered; 0.1 unit per kilogram of body weight was just as productive of exaggerated responses as the initially employed 10 unit dose.

Epinephrine Tolerance Test: It is generally accepted that a normal response is characterized by an elevation of blood sugar to 30 to 40 mgm. per cent above the fasting level in 30 to 60 minutes after epinephrine administration with a return to the fasting value by the end of two hours (12, 15). The paucity of standard figures reported and the exceptions noted in one series (13) emphasize the arbitrary character of the normal range adopted in this study: an increase of 30 *per cent* or more over and a return to within five mgm. per cent of the fasting level. Of 14 patients injected with epinephrine, three exhibited normal curves, six showed a diminished response above and a lag in returning to the base line, and five showed a normal rise in blood sugar but an abnormal, persistent elevation at the end of the test.

In general these three tests should reflect interde-

pendent and, to some extent probably, identical mechanisms. If so, the insulin and epinephrine responses should present mirror images of the same phenomenon, and the dextrose curve should represent a composite effect. Only one patient showed abnormal curves in each instance (consistent in direction). Of the remaining 11, four responded abnormally to the insulin and epinephrine, six to the epinephrine and one to the dextrose alone.

Blood serum inorganic phosphate levels are depressed by the administration of dextrose, insulin or epinephrine (12, 15, 16, 17), but few figures are available to indicate the magnitude of this change in normal individuals and the variations encountered in diseases other than diabetes mellitus. Accordingly, purely arbitrary figures are selected for classifying the inorganic phosphate response to the injection of each of the substances tested. A depression of at least 10 *per cent* below the fasting level in the cases of the dextrose and epinephrine and of 15 *per cent* in the case of the insulin is regarded as normal. Indices of exaggerated responses do not seem warranted.

On the basis of these criteria, nine patients showed a normal response of serum inorganic phosphate to the injection of dextrose, and eight less than normal. All 14 who received insulin exhibited anticipated inorganic phosphate reductions, but only eight of these did so following epinephrine administration. Four individuals showed a normal response to all three substances, four to dextrose and insulin, three to insulin and epinephrine and three to insulin alone.

There was no apparent correlation between the response as measured by blood sugar curves and as indicated by serum inorganic phosphate changes, either in the same test or among different tests. Moreover, the results of these tolerance studies in general seemed in no way to reflect clinical pictures presented. If any trend existed, it seemed for patients with long-standing cirrhosis to show fewer abnormal responses than those with relatively newly manifested disease. The epinephrine tolerance test seemed most sensitive in the former group.

DISCUSSION

Abnormalities of carbohydrate metabolism in liver disease have commanded attention ever since the French and German schools differed over the interpretation of glucose tolerance tests towards the end of the last century (18). Conn et al. (19) reported six cases of early biliary cirrhosis ("ascending infectious hepatitis" secondary to cholecystitis) with severe fasting hypoglycemia and a hyperglycemic response to ingested glucose. Moore and O'Farrell (20) and Meulengracht (21) reported spontaneous hypoglycemia in association with hepatitis, and Cross and Blackford (22) observed it following neoarsphenamine therapy. Nadler and Wolfer (23) found hypoglycemia to be the only evidence of liver dysfunction in a case of primary hepatic carcinoma, and Rank and Zelson (24) and Van Creveld (25) described comparable irregularities in glycogen storage disease (von Gierke's). Severe burns have been noted by Wolff, Elkington and Rhoads (26) to be associated with impaired dextrose tolerance due to "secondary liver damage." Moreover, diabetes has been found to disappear during the development of cirrhosis (27). Although the mechanisms responsible for these phenomena are not wholly understood, the practical implications of the problem have long been reflected in improved management of cases requiring surgery of the biliary tract (28, 29, 30, 31).

The oral dextrose tolerance test has been most widely employed in studies of liver function — sometimes with modifications such as those of Althausen et al .(32), involving insulin and water administration as well. Utilizing intravenous technique, Wilson (33) noted a low peak, sudden initial drop and a very delayed return to the fasting bood sugar level in five patients with cirrhosis of the liver — a response he did not regard as diagnostic. More recently, Tagnon and Campbell (34) performed the intravenous tolerance test in 25 patients with cirrhosis and obtained normal curves in 15, a diminished response in six and an exaggerated (late hypoglycemic) type in four.

These and other reports emphasize the variety of dextrose tolerance curves manifested in liver disease (without demonstrable relationship to the severity of hepatic derangement) and the frequency of normal patterns in the presence of well established disease processes. Such findings, while seeming to preclude a "characteristic response" in cirrhosis and related disorders, are not necessarily inconsistent with the animal and clinical experiments of Conn et al. (19), Williams and Dick (35), Soskin and his group (36, 37, 38, 39, 40) and Althausen (41), which showed that widely differing dextrose tolerance curves may in fact reflect the same pathological process in the liver, but seem to depend on the degree of damage present. Early parenchymal involvement is evidently associated with a "hyperirritability" of liver cells (Whipple Pergthal and Clark (42)), causing an initial diabetic type of curve, which, with further injury, yields to a normal curve before the even later pattern of an unresponsive liver. Hepatic rather than peripheral muscle mechanisms seem definitely to be implicated in view of the demonstration by Friedenson et al. (43) that normal arterial-venous blood sugar relationships obtain in liver disease.

Although increased sensitivity to insulin is often stressed as characteristic of hepatic disorders, the results in this test were similar to those achieved in the dextrose study; increased as well as decreased tolerance was demonstrated. That this phenomenon, too, may well indicate different stages of liver involvement is suggested by the report of Judd, Kepler and Rynearson (44), in which a patient with a "fatty metamorphosis of the liver" exhibited a prolonged phase of insulin resistance prior to the onset of a condition of spontaneous hypoglycemia. Soskin (37) related the degree of insulin sensitivity to the phase of hepatic disturbance.

The curves demonstrated by the epinephrine tolerance test were most consistently abnormal. Loeb et

al. (45) were not impressed by the blood sugar responses noted in liver disease, but subcutaneous administration as employed by them may not so readily lend itself to optimal results. On the other hand, Sucksdorff (47) noted an abnormally low rise in the blood sugar of 12 cases of acute hepatitis, one of acute yellow atrophy and one of diffuse hepatic carcinomatosis. Rank and Zelson (24) and Van Creveld (25) reported similar results in their studies of glycogen storage disease. Markowitz (47) found the onset of epinephrine induced hyperglycemia in rabbits to be dependent upon the glycogen content of the liver.

It must be emphasized that, in contrast to diffuse hepatitis, the cirrhotic liver usually contains areas of apparently normally functioning parenchyma, that curve patterns have not yet been adequately established for normal subjects and that a variety of responses to each of the three tolerance tests is evidently consistent with prevailing physiologic concepts and reported experience. Nevertheless, it is difficult to explain the lack of correlation among them. In a given instance one test might be more sensitive than the others, but, although separate mechanisms are apparently involved in hepatic storage and breakdown of glycogen (48), both processes should, to some extent, be measured by each of the substances injected. Responses in kind, if not necessarily in degree, should result. This did not occur, however; patients with increased sensitivity to insulin did not always exhibit a terminal hypoglycemia in the dextrose tolerance test, nor a rapid return to preinjection levels after an epinephrine stimulated elevation. In general, the results of one test could not be used to predict either the nature or the magnitude of the responses in the other two.

Similarly with respect to the serum inorganic phosphate curves; although insulin produced significant reductions below fasting levels in every patient, dextrose and epinephrine often failed to effect appreciable changes. Moreover, where sugar and inorganic phosphate levels were simultaneously altered, no constant quantitative relationship was observed. The fall in serum inorganic phosphate induced by dextrose in liver disease may represent a point of differentiation between true diabetic curves and the hypoglycemic response sometimes noted in hepatic disorders.

The findings indicate that these tests, singly or even collectively are not adequate criteria of hepatic cirrhosis. Selective injury of the liver with respect to certain metabolic processes apparently precludes the adoption of any one test as a dependable index of functional impairment.

SUMMARY

1. Intravenous dextrose, intravenous insulin and intramuscular epinephrine tolerance tests were performed in a group of patients with cirrhosis of the liver and the responses classified according to the nature of the venous blood sugar changes induced. Serum inorganic phosphate levels were simultaneously determined.

2. Of 17 who received intravenous dextrose, 12 showed a normal, three a diminished (pseudo-diabetic) and two an exaggerated response. Of 14 receiving intravenous insulin, six yielded normal, four diminished and four exaggerated responses. Of these same 14, 11 exhibited an abnormal and three a normal tolerance curve to the intramuscular injection of epinephrine.

3. There was no apparent consistent correlation among the results in the three tests employed, nor were parallel changes exhibited between blood sugar and serum inorganic phosphate curves.

4. While an abnormal response to intramuscularly injected epinephrine is most frequently observed, none of the tolerance tests performed appears to be a reliable index of disturbed hepatic function or of the degree or duration of liver damage present in patients with cirrhosis.

* The author expresses his appreciation to Dr. Arthur J. Patek, Jr. for his guidance in the conduction of this study.

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Volume 16
Number 5

An Unusual Case of a Perforated Littre Femoral Hernia.

By

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CASE REPORT

MRS. C. K. AGED 61, was admitted to the hospital at 1:00 A. M., November 12, 1947. Since the sudden death of her husband eight months previously, she had been in a mental institution in upstate New York for a recurrent attack of manic depressive psychosis (depressive phase). Approximately six weeks ago it was noted that she had a right femoral hernia which could be easily reduced. Seventy-two hours prior to admission to the hospital she developed an incarceration of the hernia, and an attempt at reduction was unsuccessful. There was moderate vomiting. During this period she had several loose bowel movements. About 24 hours prior to hospital admission temperature rose and her condition became grave. A surgeon, who was called in to see her, refused to submit her to surgery for fear that she would be unable to withstand the ordeal. Despite this, however, her family members insisted upon transporting her by ambulance to a hospital in New York City.

Examination: Mentality fairly good. Temperature 102.4° F.; pulse 110. Moderate dehydration. Visible peristalsis around umbilicus, but little abdominal distension. The chest revealed an area of bronchial breathing over the right base posteriorly. Blood pressure 104/70. Rectal digital examination showed an empty ampulla.

There was an area of brawny induration involving the anterior and medial aspects of the right thigh, which extended from the groin to the juncture of the of the middle and lower thirds of the thigh. The skin over this region was dusky-red and felt hot to the touch (Fig 1). Crepitation could be elicited over the area of Scarpa's triangle.

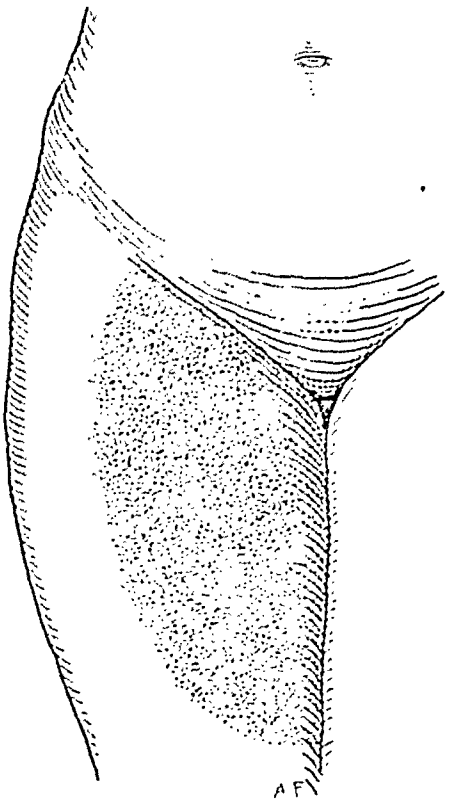


Fig. 1. — Artist's conception of findings prior to operation, showing area of thigh involved in inflammatory process.

Presurgical impression: At this time it was my impression that the patient had a perforated, strangulated femoral hernia (Littré's) with a phlegmon of the thigh due to spillage of intestinal contents, and a septic thrombophlebitis leading to embolization of the right lung. My impression was that the patient could not successfully withstand surgery without preliminary preparation. Orders were therefore given that she receive massive doses of penicillin and streptomycin, intravenous saline and plasma. A Levine tube was used.

Operation (8:00 A. M., November 12, 1947). Under gas-oxygen-ether anesthesia a six-inch right inguinal incision was made, extending to the midline of the abdomen. The distended external iliac vein was exposed extraperitoneally and isolated for a distance of two inches to permit its loose encirclement with two heavy silk ligatures, one placed distally and the other proximally. With the distal ligature held taut the anterior wall of the vein was partly incised transversely. Careful exploration of the vein's lumen proximally and distally failed to reveal the presence of a thrombus. The ligatures were then tied and the vein completely transected. Transfixation ligatures of silk were then passed through the divided ends of the vein and tied (Fig. 2).

The peritoneum was now opened and the patient placed in high Trendelenberg position. By means of moist saline packs the intestines were placed into the upper abdomen, and the region of the femoral canal was exposed. A loop of small bowel was found closely adherent to the femoral ring, from which it was dislodged by gentle traction. Upon withdrawing the loop of intestine from the abdomen, it was noted that a perforation, large enough to admit the tip of the index finger, was present at the apex of the loop on its ante-mesenteric border (Fig. 3). Although the perforation was closed in the usual manner, careful inspection of the loop left the impression that the lumen of the bowel might be sufficiently involved to lead to subsequent obstruction. A side-to side enteroanastomosis was therefore carried out between the two arms of the affected loop (Fig. 4). Owing to

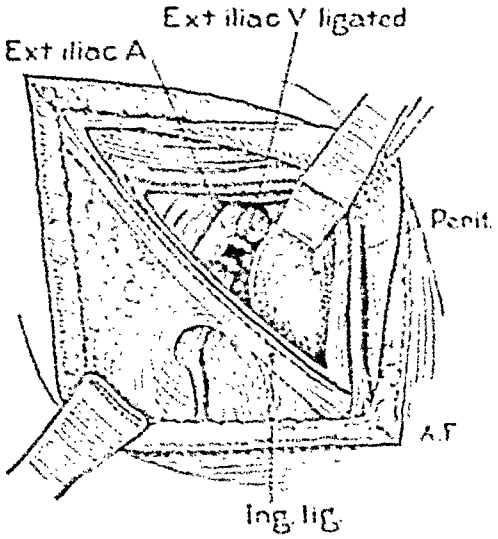


Fig. 2. — Drawing showing line of incison and extra-peritoneal exposure of external iliac vein ligated and divided.

the necrotic condition of the structures forming the femoral ring, closure was not attempted. The abdomen was closed in layers with interrupted cotton sutures.

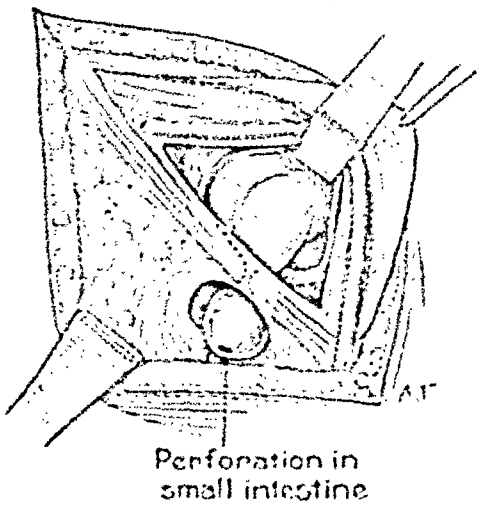


Fig. 3. — Schematic drawing showing appearance of Richter's hernia with perforation in region of fossa ovalis.

Following the aforementioned procedure, three long deep vertical incisions were made through the indurated tissues of the right thigh, and carried down to the muscles. There was an escape of gas bubbles and foul-smelling seropurulent exudate. Tissue necrosis was evident throughout the extent of the wound. Cultures and smears showed Streptococcus fecalis. As much of the necrotic tissue as possible was excised and two grams of sulfanilamide powder were placed in the wounds, which were then lightly packed with gauze. Two rubber tubes were introduced through the lateral incisions running paralled to the main midline incision.

Postsurgical course: November 14, 1947 — temperature 101.4° F. Abdominal wound clean. Loose stool coming through rectal tube. Examination of right thigh shows extreme induration, redness and pitting

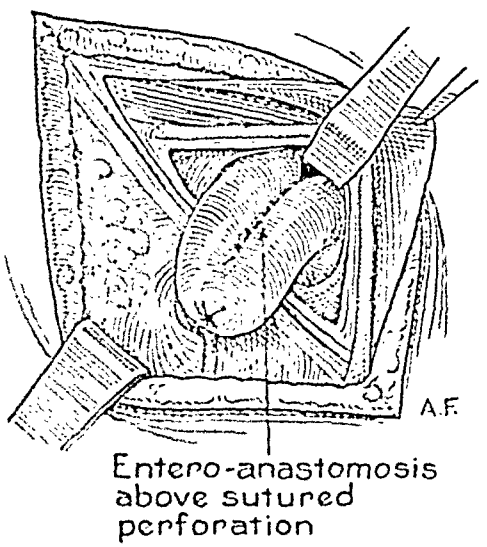


Fig. 4. — Drawing showing closure of perforation and entero-anastomosis as seen above Poupart's ligament.

edema lateral to wound. Under gas-oxygen anesthesia two additional vertical incisions were made over the indurated area. These were undermined and the area between them packed with azochloramide-saturated gauze. Patient receiving continuous intravenous drip. Streptomycin 500,000 units, and penicillin 100,000 units intramuscularly every three hours for a total dosage of 7,550,000 units of streptomycin, and 4,430,000 units of penicillin.

During the next five days two transfusions (500 cc. each) and two (1,000 cc. each) were administered. Ambulation was started 24 hours after surgery despite the presence of a moderate elevation of temperature (101° F.) which persisted for several days. There was little edema of the right leg during the entire post-surgical period.

The abdominal wound healed promptly, but sloughing of the thigh continued for four weeks. An attempt to close the skin defect in the thigh by means of shifting flaps proved unsuccessful. A full thickness graft was then taken from the abdominal wall which, while partly successful, had to be supplemented by pinch grafts. When last seen on February 27, 1948, patient was in excellent condition; wounds were healed.

COMMENT

The purpose of this paper is to record a case of strangulated perforated Littré (Richter's) hernia with a number of unusual features. A correct presurgical diagnosis was made after careful appraisal of certain suggestive symptoms and physical signs.

We have here a patient with a history of a reducible femoral hernia of six weeks' duration. However, another protrusion was noted two weeks later, which was again reduced, only to become incarcerated 72 hours prior to admission to hospital. Despite the apparent symptoms of strangulation, the presence of liquid bowel movements indicated that it was incomplete. The brawny induration of the right thigh extending downward from the groin, associated with crepi-

tation and fever, could be explained only on the basis of an infection directly associated with the femoral hernia. This would indicate a perforation of a part of the bowel wall incarcerated in the femoral ring, with intestinal contents escaping into the cellular tissue of the thigh. In order to associate the chest signs with the pathologic condition herein described, it was necessary to postulate that we were dealing with a pulmonary infarct arising from a thrombophlebitis which had its origin within the infected thigh.

Although there is a diversity of opinion among surgeons concerning the best surgical approach to repair femoral hernia, it has been customary with me to reach these herniae from above the inguinal ligament. It seems that in the example which I cite, no other choice was possible because of the infection of the thigh. The extraperitoneal approach to the iliac vessels through a Gibson incision was accomplished quickly and easily. The transperitoneal route for the reduction of the hernia and the correct handling of the perforated small intestine through one incision was not only practical, but ideal.

Apparently the administration of massive doses of penicillin and streptomycin during the pre- and post-surgical periods played an important role in the eventual recovery of the patient.

CONCLUSIONS

Perforation of a Littré hernia into the thigh, leading to gangrenous cellulitis, thrombophlebitis and pulmonary embolization is a condition rarely described in current surgical literature. A long Gibson incision is ideally suited not only to obtain adequate extraperitoneal exposure of and the proper dealing with the iliac veins, but also to the simultaneous exposure and treatment of the hernia transperitoneally. Through this incision it is possible to carry out necessary procedures to close the intestinal perforation and to restore bowel continuity, without incurring the risk of wound contamination from an adjacent area of infection, namely the thigh. The administration of massive doses of streptomycin and penicillin is of inestimable value in the post-surgical management of this variety of complicated femoral hernia.

NUTRITION

Newer Studies of Iron Ascorbate.

By

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THE DEMONSTRATION that iron is transported in plasma or serum by Moore, Doan and Arrowsmith made evident the importance of a satisfactory iron preparation for intravenous as well as oral use. However, when iron preparations are introduced intravenously Moore, Bierman, Minnich and Arrowsmith observed a marked drop in serum vitamin C level.

In view of the fact that both iron and ascorbic acid are basic factors in the oxidation-reduction mechanism of the body, a close interrelationship between the two was natural to expect. Since the absorption of iron from the intestinal tract was dependent upon the iron being in the ferrous state it became evident that the role of ascorbic acid in reducing the ferric ion to the ferrous could be very important. This was strikingly demonstrated by Moore et al. who showed that the serum iron level was not elevated after ferric chloride feeding but promptly rose after the administration of ascorbic acid. The serum iron level remained higher than after ferrous sulfate administration.

It has been shown by McFarlane that iron is transported in the oxidized state but that before it can be removed by the liver and associated storage depots it must be reduced again to the ferrous form. He presented experimental data to show that ascorbic acid may play a role in effecting this tissue reduction of the metal.

Moore et al. have shown that when soluble ferrous and ferric salts are injected intravenously into dogs, the iron disappears slowly from the blood stream during a period of 8-10 or more hours. However, it was noted that there was a prompt precipitous fall in plasma ascorbic acid at the time of the iron injection. If as much as one mg. of elemental iron per kilo body weight were injected the titratable ascorbic acid normally present in dog's plasma completely disappeared.

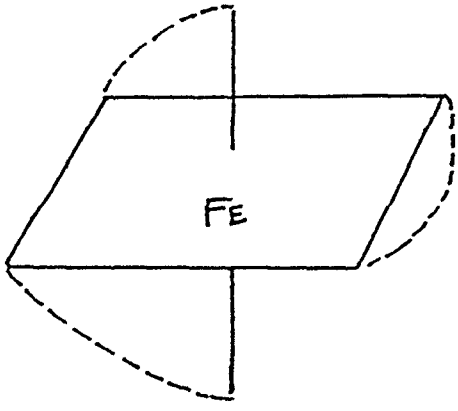
It has also been shown by Barron, Demeio and

This investigation was conducted under a grant from the Physiological Chemicals Company, Inc., who also supplied the ferrous ascorbate (Ferro-C) used in these experiments.

Submitted, October 23, 1948.

Klemperer that aqueous solutions of iron salts in the small concentrations varying .004 to .01 millimoles do not oxidize ascorbic acid. The fall in plasma ascorbic acid which occurred coincident with the intravenous injection of iron led us to seek a possible chemical explanation for the reaction.

From our studies it appears that the iron reacts with the ascorbate radical to form a ferri-ferro complex of the fromula Fe x (Fe $C_6H_6O_6$)) y in which the iron outside the bracket may be ferric (or ferrous) iron and the iron within may be ferrous (or ferric) iron. The ascorbic acid may be arranged as a dibasic acid due to its two enolic hydroxyls in similar arrangement to that proposed for oxalic acid around the ferrous or ferric atom as in Figure 1.



Ruskin first prepared iron ascorbate for therapeutic use in 1933.

Szent-Györgyi described the dark purple color which developed on exposing a solution of ferrous sulfate and ascorbic acid to air and stated that the oxidized form was colored while on reduction with hydrosulfite, a colorless leuco base was obtained. We also obtained a colorless solution on treating a solution of iron ascorbate with a solution of sodium hydrosulfite, when the pH was 7.1 within the hydrogen ion concentration range for color. We believe the formula we suggest is the probable structure in which part of the iron is in the ferric and part in the ferrous state.

The iron ascorbate we prepared had an iron content of between 19 to 20% compared to the values obtained by Maurer and Scheidt who reported 20 to 24%. On drying the iron ascorbate in vacuum over phosphorus pentoxide at the temperature of boiling toluol we obtained a loss ascribed to moisture of 12.1% when heated for three hours. With longer heating the apparent moisture was increased to 13.85% and there may still be water of hydration held which is only lost at higher temperatures at which the ascorbate would be decomposed.

The specific rotation of the iron ascorbate was +15.6 when 0.8 g. of the iron complex was dissolved in 50 ml. n H_2SO_4 at which acidity the solution is decolorized and the rotation of the ascorbic acid is obtained. This is similar to the specific rotation reported by Maurer and Scheidt.

The pH of a one per cent aqueous solution was 6.1. Titration for ascorbic acid showed 16.2% when iron ascorbate was dissolved in 8% acetic acid and an aliquot was titrated with 2, 6-dichlorobenzenone-indophenol solution. When, however, sodium fluoride was added before acidifying with acetic acid to prevent oxidation of ascorbic acid by any ferric iron present, the titration showed 24.0% ascorbic acid.

Loss of titratable ascorbic acid need not mean an actual loss of antiscorbutic power as our investigations show that much of the ascorbic acid is in the dehydro state.

We were further interested to observe the difference between iron ascorbate and ferrous and ferric sulphate added in aqueous solution to ascorbic acid. One outstanding difference was that of the pH which is 6.1 for iron ascorbate and approximately pH 2.8 for ferrous or ferric sulphate in solution with ascorbic acid. The free sulphuric acid resulting from the reaction is responsible for the low pH. Watson has shown that sulphuric acid attacks the blood porphyrins and implied that the injection of ferrous or ferric sulphates intravenously would not be desirable. The use of iron ascorbate by the intravenous route has already been successfully employed by Pijoan, Friend and Heilmeyer.

We have made a series of titrations of ascorbic acid in solutions to which ferrous or ferric sulphate was added to ascorbic acid in order to determine the effect of iron on titration of ascorbic acid with 2, 6-dichlorobenzenone indophenol.

McFarlane determined ferric ion in solution by titration with titanous chloride. He found that when ascorbic acid was added to ferric chloride in solution that one mole ascorbic acid reduced two atoms of ferric iron at pH 5.5. When ferric chloride was added to Sorensen's buffer solution at pH above 6.0, the iron was precipitated and ascorbic acid failed to reduce the iron. This may be an added explanation for the lack of effectiveness of ferric salts as antianemic agents under some conditions.

Gauron and Berg investigated the titration of ascorbic acid with dichlorobenzenone-indophenol in the presence of ferrous and ferric salts. They found that ferrous sulphate without ascorbic acid reduced the dye when titrated in the presence of metaphosphoric acid but did not effect the dye when titrated with 8% acetic acid alone. When ascorbic acid was titrated with ferrous sulphate in 8% acetic acid solution alone an accurate determination of the ascorbic acid was obtained with the dye.

However, when ferric sulphate was present, titration of ascorbic acid with the dye gave results about one-third too low in acetic acid alone. When metaphosphoric acid solution was added, however, the titration with the dye gave values in agreement with the ascorbic acid added. They concluded that the dye reduced by ascorbic acid is reoxidized in the presence of the ferric ion in acetic acid alone and that metaphosphoric acid forms a complex with the

ferric ion which prevents the reoxidization. They discarded the lower titration value of ascorbic acid obtained in acetic acid when ferric iron was present. We believe these investigators overlooked the tendency of ferric iron to oxidize the ascorbic acid to dehydro-ascorbic acid in acid solution and these lower titration values were correct, while the higher titration values with metaphosphoric acid present were due to the reduction of ferric to ferrous iron, the latter reducing the dye further in the titration of ascorbic acid.

In further investigation of the titration of ascorbic acid with 2, 6-dichlorobenzenone in the presence of ferric and ferrous iron we used the following procedure.

TITRATION OF ASCORBIC ACID WITH 2, 6 DICHLORO-BENZENONE INDOPHENOL.

Four g. of ascorbic acid was dissolved in water and made to a volume of 1,000 ml. Three and four-tenths g. of ferric sulphate was dissolved in water and made to a volume of 1,000 ml. Two and six-tenths g. of anhydrous ferrous sulphate was dissolved in water with five ml. concentrated sulphuric acid and made to a volume of 1,000 ml. Twenty-five ml. of ascorbic acid solution was pipetted into each of three 100 ml. graduated flasks. In one flask it was made up to 100 ml. volume with water; in another it was combined with 25 ml. of the ferric sulfate solution before making up to volume with water. In the third flask it was made up to volume after adding 25 ml. of the ferrous sulfate solution and sufficient sodium hydroxide solution to bring to pH of 2.5. Two ml. of the diluted solutions were titrated with the dye after adding five ml. of metaphosphoric-acetic acid solution or five ml. of 8% acetic acid solution.

Titration in Presence of Ferric Iron

Ascorbic Acid Sol.	$Fe_2(SO_4)_3$ Sol.	2, 6 Dichlorobenzenone Indophenol (Required for end point)	
ml.	ml.	ml.	
		Acetic Acid +HPO_3	Acetic Acid Alone
00	25	0.10	0.10
25	00	16.0	16.02
25	25	15.65	9.60

In the titration of ascorbic acid in acetic acid alone the amount of dye solution required to oxidize the ascorbic acid is decreased considerably when ferric iron is present, indicating oxidation of ascorbic acid by the ferric iron. The difference in titration of the ascorbic acid with and without ferric iron corresponds approximately to the oxidation of one mole ascorbic acid by two atoms ferric iron in agreement with the ratio found by McFarlane in acid solution.

When metaphosphoric acid was added before titration the titration did not show oxidation of the ascorbic acid although the ferric sulfate and ascorbic acid had been combined before addition of the metaphosphoric acid and could not have protected the ascorbic acid from oxidation. We have already suggested that ferrous iron had been formed and resulted in further reduction of the dye solution.

Titration in Presence of Ferrous Iron

Ascorbic Acid Sol.	Fe_2SO_4 Sol.	2, 6-Dichlorobenzenone Indophenol ml.	
ml.	ml.		
		Acetic Acid +HPO_3	Acetic Acid Alone
00	25	3.65	0.10
25	00	15.83	15.80
25	25	19.15	14.75

In the titration of ferrous sulfate with the dye solution, the ferrous sulfate reduced the dye when no ascorbic acid was present when titrated with metaphosphoric acid-acetic acid solution as previously shown by Gauron and Berg, while in acetic acid alone the dye was not reduced by ferrous sulfate since 0.10 ml. was required for the color end point. The hydroxyls of the metaphosphoric acid appear to have the same effect as hydroxy organic acids on the reduction of the dye by ferrous salt as observed by Basu and Nath.

When ascorbic acid was titrated with ferrous sulfate in acetic acid solution with no metaphosphoric acid present, the titration value was a little less than when no ferrous sulfate was added, the difference probably being due to some ferric iron in the ferrous sulfate solution.

We may conclude that titration with 2, 6-dichlorobenzenone indophenol of ascorbic acid in solution with either ferric or ferrous iron in acetic acid solution gives the actual value of ascorbic acid in solution, while addition of metaphosphoric acid results in erroneous increase in titration values.

If the effect of the ferric ion is to oxidize the ascorbic acid to dehydroascorbic acid, thus decreasing the amount of dye solution required to oxidize the ascorbic acid, it occurred to us that the addition of fluoride ion to repress the ferric ion would indicate the nature of the reaction. Peters has shown that fluoride ion forms a complex with ferric ion which sharply represses the concentration of ferric ion in oxidation reduction reactions.

Twenty-five ml. of ascorbic acid solution (four g. ascorbic acid to 1,000 ml. with 8% acetic acid) was diluted to 100 ml. with 8% acetic acid, and 25 ml. of ferric sulphate solution as previously made was diluted separately to 100 ml. with n/10 sulfuric acid solution.

Two ml. of the diluted ascorbic acid and five ml. 8% acetic acid required 16.10 ml. dye solution.

Two ml. of ascorbic acid solution plus two ml. ferric sulphate solution required 9.90 ml. dye solution.

Two ml. of ascorbic acid plus two ml. of ferric

sulphate mixed and then .50 g. of sodium fluoride added required 10.9 ml. dye solution.

Two ml. ascorbic acid and .50 g. sodium fluoride mixed, then two ml. ferric sulphate solution added required 16.00 ml. dye solution.

These results indicate that the sodium fluoride prevented the oxidation of the ascorbic acid by ferric sulphate if added before the ferric salt was mixed with the ascorbic acid solution.

When the sodium fluoride was added first to ascorbic acid solution and ferrous sulphate instead of the ferric salt added there was a slight increase of dye solution required of about 0.5 ml. over that required for the ascorbic acid without sodium fluoride.

McFarlane observed that when ferric chloride was added to Sorensen's phosphate buffer solution the iron was precipitated above pH 6 and the precipitated iron did not oxidize ascorbic acid as it did at a lower pH range. His iron determinations were made with titanous chloride.

We have made some titrations which show that ferric iron does not immediately oxidize ascorbic acid at pH 6.8.

Ascorbic acid solutions and ferric sulphate solutions were prepared as previously described. Twenty-five ml. of ascorbic acid solution was pipetted into a 100 ml. volumetric flask and sufficient sodium hydroxide solution added to bring the solution to a pH of 7.0 as determined on a separate portion. To twenty-five ml. of the ferric sulphate solution in a beaker was added sufficient sodium hydroxide to bring it to a pH of 7.1, the ferric iron mixture in which iron had precipitated was washed into the flask containing the ascorbic acid and the volume made to 100 ml. with water. The pH of the combined ascorbic acid and ferric iron was 6.8. Some iron precipitate remained after mixing.

Two ml. of the ascorbic acid-ferric iron mixture was titrated with 2, 6-dichlorobenzenone indophenol but 0.5 g. sodium fluoride was added before addition of acetic acid to protect from oxidation on acidifying. The titration required 16.05 ml. dye solution showing almost no oxidation had taken place at pH 6.8 since two ml. of diluted ascorbic acid without ferric sulphate had required 16.35 ml. dye solution.

When no sodium fluoride was added to the ascorbic acid-ferric iron mixture, two ml. of the mixture acidified with five ml. acetic acid required only 8.35 ml. dye solution, showing oxidation occurring after acidifying.

When the ascorbic acid-ferric iron mixture stood over night in a stoppered flask at room temperature, or was heated at 70° in a water bath for 10 minutes, titration with sodium fluoride added before acidifying showed that slow oxidation had occurred at pH 6.8 under these conditions.

When heated in a boiling water bath for five minutes and cooled, the iron precipitate was completely dissolved indicating formation of an iron complex.

The effect of ferric and ferrous iron on the specific rotation of ascorbic acid was determined to obtain indications of formation of dehydroascorbic acid which has a specific rotation of +56. compared to +25. of ascorbic acid. These rotations were made at room temperature and are only relative. The acidity of the solutions was about pH 1.4, and such that the solutions showed no blue color.

2 g. ascorbic acid made to volume of 100 ml. with water +23.8.
2 g. ascorbic acid +1.7 g. ferric sulphate to 100 ml. with water +32.5.
2 g. ascorbic acid +3.4 g. ferric sulphate to 100 ml. +40.0.
2 g. ascorbic acid +5.1 g. ferric sulphate to 100 ml. +48.7.

The increase in specific rotations as shown above is in agreement with expected increases in dehydro-ascorbic acid due to oxidation of ascorbic acid by the ferric ion.

On standing these iron solutions mutarotated and the specific rotation decreased considerably.

When 2.6 g. ferrous sulphate was added to the ascorbic acid solution, the specific rotation was +25. indicating little effect on the specific rotations of the ascorbic acid.

IRON ASCORBATE

When we analyzed the blue black compound of iron ascorbate, we applied what we had learned from the titration of the solutions described above.

Two g. of ferrous ascorbate was dissolved in 400 ml. of water and filtered from a very slight residue. Fifty ml. of the solution was diluted to 100 ml. with acetic acid and water to make an 8% solution of acetic acid. Titration of two ml. of this solution with the dye solution gave a value of 16.2% ascorbic acid.

Since the iron ascorbate appears to contain some iron in the ferric state, one ml. of the aqueous solution was mixed with 0.5 g. sodium fluoride to prevent oxidation of ascorbic acid by ferric iron on acidifying with 8% acetic acid. The titration then indicated 24.0% ascorbic acid in the iron ascorbate.

Two hundred ml. of the original solution was saturated with hydrogen sulfide and three ml. of concentrated ammonium hydroxide was added to make it slightly alkaline and hydrogen sulfide bubbled through for 30 minutes. It was filtered clear of iron sulfide. To 100 ml. of the filtrate was added 10 ml. of acetic acid and nitrogen gas bubbled through to remove the hydrogen sulfide. The solution was filtered from separated sulphur. Titration of the clear filtrate gave a value of 37.4% ascorbic acid, an increase of 13.4% of ascorbic acid, due probably to reduction of dehydroascorbic acid by hydrogen sulfide and an indication that dehydroascorbic acid is present in the iron ascorbate.

The specific rotation of iron ascorbate in dilute sul-

phuric acid to decolorize the solution was +15.6.

After treatment of the iron ascorbate solution with hydrogen sulfide and removal of iron the *specific rotation* was +7.5 at pH 1.5, indicating again the reduction of dehydroascorbic acid with its higher specific rotation to ascorbic acid with its lower rotation.

Maurer and Scheidt obtained 40% ascorbic acid in iron ascorbate after treatment of the solution with hydrogen sulfide and titration of the solution with iodine after removal of hydrogen sulfide. These investigators determined no value for ascorbic acid before hydrogen sulfide treatment.

In order to correlate our value for ascorbic and dehydroascorbic acid, we proceeded to make the 2, 4-dinitrophenyl (osazone) in a portion of solution that had been treated with hydrogen sulfide to remove the iron with subsequent removal of the hydrogen sulfide. A portion representing 0.1 g. iron ascorbate was heated with a solution of 0.4 g. 2, 4-dinitrophenylhydrazine in 250 ml. 2 normal hydrochloric acid at 70° for five hours. After standing over night, it was filtered and washed with dilute hydrochloric acid and then with water. The dry osazone weighed 0.1150 g. equivalent to 0.0343 g. of ascorbic acid, which in percentage of iron ascorbate as ascorbic acid would be 34.3% in good agreement with the value we obtained by the titration method. Herbert, et al. first prepared this osazone from ascorbic acid and from dehydroascorbic acid and Penney and Zilva obtained it also from l-diketogulonic acid and showed that from 70 to 85% of either the ascorbic acid or its two derivatives could be recovered as the osazone.

Our value for the osazone of 34.3% calculated as ascorbic acid may be therefore increased about 20% for the entire amount of ascorbic acid, dehydroascorbic acid and l-diketogulonic acid in the iron ascorbate and after deduction of the value obtained by the titration method indicates but little if any l-diketogulonic acid in the compound. However, Penney and Zilva have shown that l-diketogulonic acid in the presence of hydrogen sulfide at pH 7.4 undergoes an irreversible change and further investigation is required to determine if l-diketogulonic acid has been overlooked in our preparation of the osazone.

The therapeutic effectiveness of iron ascorbate indicates its important role in the oxidation-reduction processes of the body. The titration studies also throw more light on the mechanism of the drop in ascorbic acid plasma levels after the introduction of the ferric ion into the blood stream. Apparently about half may be accounted for as dehydro ascorbic acid which is reversibly reduced to ascorbic acid after a period of time. The introduction of iron ascorbate may avoid this plasma C level drop.

The better tolerance of iron ascorbate both by mouth and intravenously indicates the physiological nature of the compound.

The case records of Heilemyer give dramatic support to this conception.

The animal experiments recorded in the British literature by Dehn give an interesting comparison between iron ascorbate, reduced iron and saccharated iron.

Dale G. Friend of the Medical Division of the Peter Bent Brigham Hospital in Boston also showed that iron ascorbate can be given intravenously and retains enough vitamin C activity to make it doubly valuable in cases of anemia associated with subnormal levels of vitamin C such as scurvy, duodenal ulcer and nutritional anemia. Intravenously, it appears to be as effective in doses of 10 mg. of iron as is 32 mg. of iron as iron and ammonium citrate. Orally 200 to 300 mg. of iron as iron ascorbate is as effective as is 1,000 mg. of reduced iron or 4,000 to 6,000 mg. as iron ammonium citrate. Friend completely confirmed the strikingly effective results of Heilmeyer.

It has become apparent that quality of iron compounds plays an important role similar to that now realized for proteins. Its biological activity should guide its value just as we rate protein hydrolysates with lactalbumin as 100%, casein at 73%, beef at 78%, etc. Simply prescribing large doses of ferrous sulphate or iron ammonium citrate is not necessarily harmless. Fowler and Barer showed that with the oral administration of iron and ammonium citrate to patients with hypochromic anemia large amounts are retained by the body. An average of 32.6% of the iron administered was retained by the body. Approximately 1.9% of the iron administered was utilized in the formation of hemoglobin. There was no correlation between the amount of iron retained and the increase in the hemoglobin content. They suggest that the accumulation of this iron in the liver can be considered dangerous and may play a role in causing iron cirrhosis. The iron content of the liver can be increased to eight times the normal value.

Pijoan in the surgical division of the Peter Bent Brigham Hospital points out that the successful use of ferrous ascorbic acid in the treatment of secondary anemias has already been recognized to some extent.

His investigation showed that ferrous ascorbate was nontoxic when administered intravenously to either experimental animal or human subjects and has been employed in his clinic for the treatment of secondary anemia. This salt was found by them to have a highly antiscorbutic property when given intravenously daily over a period of six days to a patient with severe scurvy. A daily dose of 250 mg. was sufficient to bring the plasma ascorbic acid level from .02 mgm. per cent to 1.2 mgm. per cent and the disappearance of marked scorbutic symptoms.

Pijoan with the cooperation of Dr. Alexander and Dr. Townsend confirmed these findings in guinea pigs and in normal subjects. "An interesting feature in the use of the salt, as is especially demonstrated in normal subjects, is the slow rise in the plasma ascorbic acid content as determined by the method

of Pijoan and Klemperer following its intravenous injection as contrasted to the slope of the values obtained after the injections of ascorbic acid. It would appear from these biological tests that the compound of iron ascorbate breaks down slowly."

Chemically after precipitating the ferrous ion by H_2S as ferrous sulfide and the reduction of any oxidized ascorbic acid by H_2S they reported that they obtained 97% of the calculated ascorbic acid in the iron ascorbate they had prepared. This is a much higher content than reported by Maurer and Scheidt or by us but then titration with the 2, 6-dichlorobenzenone indophenol was made in trichloracetic acid solutions in which the dye is decolorized when no ascorbic acid is present as observed by Birch, Harris and Ray and also by Bessey and King who found that titration in acetic acid gave a more definite end point.

Pijoan concludes that iron ascorbate is not only successful in bringing ferrous iron into the treatment of secondary anemias but has valuable antiscorbutic properties in which single daily doses produce prolonged and increased plasma ascorbic acid values.

How deep seated is the attraction of ascorbic acid for iron can be seen in the coupled oxidation of ascorbic acid and hemoglobin. Lemberg et al. have shown that ascorbic acid and oxyhemoglobin react directly to form choleglobin. The ascorbic acid is oxidized to dehydroascorbic acid and finally to other products. Experiments in which dehydroascorbic acid was used instead of ascorbic acid showed it was not able to form choleglobin from hemoglobin.

An experiment conducted by Lemberg throws an interesting light on the scavenger action resulting from the coupled oxidation of ascorbic acid and oxyhemoglobin. Using laked horse erythrocytes diluted to a hemoglobin concentration of 0.72% showed choleglobin formation as follows:

Conditions	Incubation time in minutes	Choleglobin in % of initial hemoglobin	
		Laked	destromatized cells Laked
pH 7.2 @ 37°	15	1.3	5.3
	30	5.1	15.
pH 8.5 @ 37°	15	22	—
	30	30	—

This experiment indicates the presence in the erythrocytes of a factor inhibiting the formation of choleglobin. When the stromata are removed by keeping the laked cells at a pH of 5.8 in the refrigerator and centrifuging, the hemoglobin of the destromatized red cells is now attacked by ascorbic acid and oxygen as rapidly as that in a solution of crystalline oxyhemoglobin. These observations help to explain the absence or slow formation of choleglobin in red cells. The concentration of ascorbic acid in red cells is considerably smaller than that necessary for the formation of choleglobin. Stephens and Hawley found 0.85 to 1.2 mg. ascorbic acid per 100 ml. in human erythrocytes. Lemberg concludes that the membrane of the red cell offers some protection to the hemoglobin contained in it by its very incomplete permeability to ascorbic acid. The protection of the plasma ascorbic acid from oxidation by the red cells is probably due to the stroma factor. The rapid destruction of ascorbic acid in the blood following hemolysis is due to the coupled oxidation with hemoglobin. Ruskin points out that the presence of dehydroascorbic acid and its level should be used as an indicator of hemolysis and hemolytic infection.

These studies also open up an interesting avenue for cancer research. The demonstration by Gross that species specific hemolysins formed or liberated by the cancer cells is responsible for the anemia in cancer patients would represent a stroma destroying factor possibly allergic in character that breaks down the barrier between oxyhemoglobin and ascorbic acid and allows the coupled oxidation on the ascorbic acid. When we correlate this observation with that made by Lemberg that choleglobin formation from oxyhemoglobin is greatly increased with low oxygen concentrations we can begin to find an explanation for the peculiar pigmented appearance of the patient with cancer anemia. It is apparent that low oxygen pressure in the tissue cells favors the oxidation of hemoglobin to choleglobin. Factors favoring the preservation of the stroma factor would be particularly helpful and in this respect the beneficial results observed empirically with calcium ascorbate (calscorbate) is worthy of serious consideration. The possible role of antihistaminics in retarding the destruction of the stroma factor is also opened up. The restoration of oxyhemoglobin which has been converted to choleglobin entails the availability of additional iron. Barkan and Shales showed that blood and hemoglobin solutions contain 5 to 6% of the total iron in the form of "labile iron." The increase of labile iron occurring during the coupled oxidation of hemoglobin and ascorbic acid is proportional to the concentration of choleglobin formed. The administration of iron ascorbate (Ferro-C) would thus provide a rapid source for hemoglobin regeneration and protect the plasma vitamin C level from preliminary conversion to dehydroascorbic acid.

SUMMARY

1. The chemical relationship between iron and the ascorbate radical was studied. The behavior of solutions of ferrous sulphate and ascorbic acid were quite different from that of ferrous ascorbate. The presence of free acid leads to a more rapid breakdown of ascorbic acid, similar to that of a high alkaline reaction. The near neutral pH of ferrous ascorbate was more stable than either extreme.

2. Iron ascorbate is a labile ferri ferro complex.

3. An explanation for the rapid drop in plasma vitamin C level after the intravenous introduction of iron is presented.

4. The role of the coupled oxidation of oxyhemoglobin and ascorbic acid and the relationship of the stroma factor to cancer anemia is pointed out.

Nutrition Notes

Nutrition Report of FAO Conference

The director of the Nutrition Division of the United Nations Food and Agriculture Organization, Dr. W. R. Aykroyd, reported at the Fourth Annual Conference of FAO in Washington, D. C., November 15-29, on the 1948 work program of the Division and said that the 1949 program would be essentially a continuation and extension.

He concluded by saying that the Nutrition Division, although small, occupies an important position in FAO, as FAO production objectives must conform with nutritional requirements. He added that effective nutritional policies designed by competent nutrition workers give direction to all activities which aim toward a stimulation of production.

The Conference approved the program outlined and requested that the recommendations made at the regional nutrition conferences at Baguio and Montevideo (October NNL) and at the Cairo conference held in February 1948 be implemented. Further regional conferences are to be arranged.

The Conference also recommended that FAO continue to cooperate actively with the United Nations International Children's Emergency Fund (June NNL).

The Division is carrying on technical studies on food composition, dietary surveys, school feeding (December NNL), nutrition education, and food technology, according to Dr. Aykroyd's report. The Conference attached special importance to those studies which develop standard methodology in, for example, dietary surveys, physiological requirements for calories and nutrients, and food composition. It recommended that the field of food composition be extended to cover the influence on nutrient content of such factors as climate, cultural conditions, and variety, and of the nutritive value of foods, especially wild plants, used by primitive and remote peoples.

The discussion of nutrition problems was continued by the Standing Advisory Committee on Nutrition which met immediately following the close of the FAO Conference.

Fifty-seven member nations sent delegates to this Conference; in addition, there were observers from nonmember nations and international organizations. Agriculture Secretary Brannan served as chairman of the Conference. It opened with a message of welcome from President Truman and he addressed it in person on November 24.

Director-General Norris E. Dodd pointed out that previous conferences of FAO have been concerned with organization and with building foundations for work. Now the organization is completed: FAO is a going concern with work begun in every field — nutrition and food management, agriculture, forestry, fishieries, rural welfare, and improvement of statistical measuring rods. Now it can settle to the long, hard pull toward accomplishment of its great design, he said.

The annual review of the state of food and agriculture provides for the necessary and continuing measurement of progress and problems. Although better 1948 crops have dulled the edge of the food crisis, we have not yet matched the growing needs of a growing world, either in the care and development of our resources, or in the application of modern science to production, or in the improvement of distribution and use of products of the soil and waters. Although study and understanding of the problem is necessary, accomplishment is secured only through action, and action must in the main come from member governments themselves.

Three printed reports were prepared for this conference: "National Progress in Food and Agriculture Programs 1948" (147 pp., $1); "The State of Food and Agriculture 1948" (216 pp., $2); and "Work of FAO 1947-48" (90 pp., $1). These may be secured from the International Documents Service, Columbia University Press, 2960 Broadway, New York 27, N. Y., at the prices indicated. A popular folder "FAO, What It Is, What It Does, How It Works," and a 21-page booklet "Facts About FAO" are available free from the Food and Agriculture Organization, 1201 Connecticut Avenue NW., Washington 25, D. C.

Nutrition Committees in Other Countries

Official national nutrition councils have been created and are functioning in 20 of the 46 countries and territories for which reports were received by the FAO, according to its report "National Progress in Food and Agriculture Programs 1948," mentioned in the foregoing article.

Some councils have been established by government decree, as in Canada, Norway, Peru, the Philippines, and the Union of South Africa. Others have developed as committees of a research council or institute. In a few countries, such as Chile, unofficial associations of nutrition workers carry out a number of the functions of a national nutrition organization. Several countries, for example, France, the United Kingdom, and Japan, have an unofficial nutrition workers' association in addition to an official organization.

The most important functions of these national nutrition organizations are to advise their governments on matters of nutrition policy and programs, and to coordinate the activities of all governmental and nongovernmental agencies engaged in nutrition work, relating them to local conditions. They have helped to solve urgent food problems and to promote scientific and educational work. Many of them are concerned with school and other supplementary feeding programs while practically all of them carry on nutrition and dietary surveys.

The Canadian Council on Nutrition in 1944 approved Canada's Food Rules as a guide to the variety and amounts of foods needed to meet all dietary requirements. Eat these foods every day and drink plenty of water.

Here are Canada's Food Rules — listing the foods for health. *Milk* — adults, 1/2 to 1 pint; children, 1 1/2 pints to 1 quart. *Fruit* — one serving of citrus fruit or tomatoes or their juices and one serving of other fruit. *Vegetables* — at least one serving of potatoes: at least two servings of other vegetables, preferably leafy, green or yellow, frequently raw. *Cereals and bread* — one serving of a whole-grain cereal and at least four slices of Canada Approved Vitamin B bread with butter. *Meat and Fish* — one serving of meat, fish poultry or meat alternates such as beans, peas, nuts, eggs or cheese. Also use eggs and cheese three times a week each, and liver frequently. A fish liver oil, as a source of vitamin D, should be given to children and expectant mothers. Iodized salt is recommended.

1. Health and Welfare: Ottawa, Canada. Nov. 1948.

Abstracts on Nutrition

HOFFMAN, W. S., PARMALEE, A. H., AND GROSSMAN, A.: *Mechanism of production of acidosis in premature infants by protein milk.* (Am. J. Dis. Child. May 1948, Vol. 75, No. 5, 637-658).

Studies of electrolyte balance and serum analyses made on three premature infants showed that a diet of unmodified powdered protein milk for three days produces a serious acidosis with elevated serum chloride and lowered serum bicarbonate levels. The balance of sodium and water is negative and the balance of potassium, calcium and phosphorus positive. These results are in corroboration of Darrow's observations.

Cation-anion partition studies of the urine on five other premature infants over a nine day period — three control days of evaporated milk diet, three days of protein milk diet and three recovery days of evaporated milk diet — demonstrated that the limited production of ammonia normally exhibited by these infants could be increased under the stress of acidosis, but that it did not reach its maximum until the recovery period. Titratable acidity and hydrogen in concentration were also increased. The chief renal limitation was the inability to concentrate the urine. In spite of the increase in base economy, there was a drain of sodium from the body to help neutralize the increased excretion of chloride, phosphate and sulfate. At the same time, less potassium was available for excretion.

Calculation of the distribution of electrolytes and water demonstrated that during the powdered protein milk period chloride retention usually produced an expansion of extracellular fluid volume. Since the balance of water and sodium was negative, these items had to be drawn from the intracellular fluid compartment for this expansion, even as Darrow had found. While sodium was being removed, the potassium content of cells increased. In the recovery period, the positive balance of water and sodium succeeded partly in reversing this process, but it was not sufficient to restore the lost sodium in muscle.

Acidosis also developed in 10 full term infants on the powdered protein milk diet, but to a less severe degree. Urine partition and balance studies on three of these infants showed that the essential differences between these and the premature infants lay (1) in the slightly more mature renal function, which allowed a greater excretion of chloride and a greater conservation of sodium, and (2) in a relatively greater reserve of water and sodium in muscle that could be drawn on to permit the expansion of extracellular fluid volume.

KINSELL, L. W., MICHAELS, G. D., BARTON, H. C. AND WEISS, H. A.: *Protein balance studies in patients with liver damage. II. The role of lipotropic agents.* (Ann. Int. Med. Nov. 1948, Vol. 29, No. 5, 881-902).

The authors found that choline and/or methionine, when given in addition to a high protein and high vitamin diet, exert a protein anabolic effect in patients with chronic liver damage. Just how much these substances help in acute hepatitis could not be decided, because of the intrinsic variability of the disease. There was no evidence that methionine had any greater effect on the protein balance than choline. Since all patients received a high protein diet, it may be that the "choline effect" was actually a methionine sparing effect. Lipotropism probably was not a main effect since biopsy sections showed a lack of fat. The use of liver extracts in cases of severe liver damage *may do harm rather than good.*

DAVIS, W. D. AND CULPEPPER, W. S.: *Cirrhosis of the liver associated with alcoholism: Report of acute exacerbation with serial liver biopsies.* (Ann. Int. Med., Nov. 1948, Vol. 29, No. 5, 942-958).

A case is presented of hepatic cirrhosis showing an acute exacerbation associated with alcoholism, in which serial liver biopsies were employed. This series shows the resolution of the severe fatty degeneration and polymorphonuclear infiltration over a period of six months, closely paralleling the clinical and laboratory signs of improvement. One remarkable feature was the presence of severe congestive cardiac failure which disappeared spontaneously with the resolution of the hepatic lesion. The treatment employed included high protein diet, hyperalimentation, methi-

of mineral elements from the blood cells into the serum and vice-versa. The chief precaution is a dry syringe and the separation of serum from clot within one hour of the time of venupuncture. The average values, given in milligrams per 100 cc. are as follows: Potassium 20.2, Sodium 335.0, Calcium 10.1, Magnesium 2.3, and Chloride 358.0. The highest level of calcium encountered was 11.5 and the lowest 9.1.

BARNETT, A. J.: *Addison's disease: report of a case with unusual features and reviews of 30 cases.* (Med. J. Australia, Dec. 25, 1948, Vol. 35, No. 26, 742-744).

The author demonstrates fairly conclusively that the essential, most frequently present, and pathognomonic features of Addison's disease are asthenia, skin pigmentation, loss of weight and gastro-intestinal symptoms such as nausea, vomiting and diarrhea. Hypotension is by no means always present and it is of particular interest to note that the blood concentrations of sodium and potassium may not vary from normal. In the case completely described, the serum content was 352 mgms. per 100 cc. and the serum potassium content was 20 mgms. per 100 cc. In the entire series, the only change of sufficient frequency to be noted in blood chemistry was a lowering of the serum sodium level. It was not possible to find any clinical distinctions between cases with normal or abnormal mineral blood levels. The author is opposed to the subcutaneous implantation of "Percorten" tablets as two deaths followed such a procedure. It would appear from Barnett's work, that the reliance sometimes placed on the blood chemistry to confirm the diagnosis of Addison's disease is perhaps ill-founded. He regards the Cutler, Power and Wilder test as reliable but dangerous inasmuch as the withdrawal of sodium is capable of precipitating a crisis.

Editorial

EVOLUTION IN PEPTIC ULCER?

Craig (1) has presented an unusual and stimulating study of the history of peptic ulceration and draws some curious and surprising conclusions. He studied the death rates from gastric and duodenal ulcers over a period of 150 years and familiarized himself with the work of medical authorities of roughly a century ago. After making due allowances for difficulties in diagnosis and confusion in reporting on the death certificates, he seems justified in stating that gastric ulcer was uncommon until the beginning of the present century. Since then both types of ulcer have increased in males, while gastric ulcer formerly common in young women, has become rare while duodenal ulcer in females has increased, and mortality from gastric ulcers in young women has shrunk to negligible proportions. Although little change can be detected in the nature of duodenal ulcer, it is clear that the pattern of gastric ulceration has altered profoundly during the past 100 years. Constitutional factors could scarcely account for these changes, and hence the changes probably depend upon changing environmental conditions. There is some support for the view that the evolution of duodenal ulcer particularly has paralleled the development of the highly civilized state of today. The highest death rate from both types of ulcer in males occurred in England about 1940 at the time of the air blitz. These findings are in line with present conceptions of peptic ulcer as the expression of emotional upset. However, the virtual disappearance of gastric ulcer as a lethal disease in young women is not so readily explained. Craig feels that gastric and duodenal ulcerations are two distinct diseases. A similar study of peptic ulcer in America would prove interesting.

REFERENCE

1. Craig, J. D.. The evolution of gastric and duodenal ulceration. Brit. Med. J., Aug. 14, 1948, 330-334.

Book Reviews

DIRECT ELECTROCARDIOGRAPHY OF THE HUMAN HEART AND INTRATHORACIC ELECTROCARDIOGRAPHY. By Groedel, Franz M. and Borchardt, Paul R. 224 pp. 29 illustrations, 38 tables. Brooklyn Medical Press, New York. 1948. $9.00

Diseases of the cardiovascular system and the gastrointestinal tract are frequently linked together and even more often is the symptomatology identical and the differential diagnosis difficult. Therefore, the gastroenterologist must keep up with the progress in cardiology and vice versa.

This book gives further proof that Groedel's theory of the individuality of the electrocardiograms of the left and right heart (as introduced in 1933) is correct. The limb leads are superimpositions of the potential variations, created asynchronously during the function of the right and left ventricle. So-called chest leads, when obtained in the way suggested by Groedel, and when taken from proper sites of the chest wall, reflect fairly accurately the electrogram (correctly: potential variations) existing at the surface of the ventricles.

Groedel and Borchardt, in order to obtain access to the surface of the heart, examined exposed hearts during chest operations and, the authors' new method, during pneumolysis. This latter mode of direct electrocardiographic heart exploration is comparatively simple and can be accomplished in about fifteen minutes.

The results of the first hundred examinations, compiled on 38 tables, are reported, and the analysis of the electrocardiogram in general and of the electrocardiograms obtained with various techniques (such as extremity, chest, unipolar limb leads) is extensively discussed.

This is the first report about the true electrogram (potential variation) at various sites of the surface of the human ventricles, auricles, the sinus node, in healthy hearts, in a few pathological conditions, and in auricular and ventricular extrasystole. The electrograms are also traced along their way over lungs, diaphragm, to the surface of the body.

The book, no doubt, has furnished the foundation for the understanding of the genesis of the human electrocardiogram. It will be equally as important for all those who wish to know what the electrocardiogram really represents as for the cardiologist.

The book is well printed, the illustrations are clear, the bibliography extensive.

FRANZ J. LUST, M.D.
NEW YORK, N. Y.

MANAGEMENT OF COMMON GASTRO-INTESTINAL DISEASES. Edited by Thomas A. Johnson. 280 pages, 16 figures and four charts. ($7.00) J. B. Lippincott Co. Philadelphia. 1948.

This is a symposium on gastro-intestinal diseases. Nineteen authors have contributed to this book. Every one of them discusses a topic on which he has A special experience. Schindler and Blomquist write a chapter on chronic gastritis which gives an excellent résumé of the author's great experience with this condition. There is another chapter by Co Tui on Treatment of intractable peptic ulcer with protein hydrolysates and we hear of Co Tui's ideas in this still contested therapy. Enterogastrone in the therapy of peptic ulcer is presented by Ivy and Grossman, and we know that this chapter could not be better presented than by these authors. Other chapters are: Keisner and Palmer on Recognition of gastric malignancy, Sarah Jordan on Diagnosis and management of benign gastric ulcer, Edward Weiss on Psychosomatic aspects of ulcer, Albert F. R. Andresen on Management of bleeding peptic ulcer, Edward Weiss on Psychosomatic aspects of gastro-intestinal disorders, Crohn and Yarnis on Present status of therapy of regional enteritis, Johnson on the diagnosis of pancreatic disease by means of determinations of serum lipase and serum amylase, and another chapter by the editor of the book on Diagnosis and management of distal ulcerative colitis. Other contributions are: Berk on Diagnosis of carcinoma of the pancreas, Tumen on Cirrhosis of the liver, Havens Jr. on Diagnosis and management of viral hepatitis, Collins on Diagnosis and treatment of irritable colon, Aaron and Milch on Carcinoma of the colon, and Bercovitz on Differential diagnosis and treatment of amebiasis and its complications.

This publication belongs to the "American Practitioner Series," however, not only the general practitioner but the specialist in this field will enjoy reading this book, even though he may disagree with some of the authors. A short bibliography is added to each chapter.

FRANZ J. LUST, M.D
NEW YORK, N. Y.

PSYCHODYNAMICS AND THE ALLERGIC PATIENT. By Harold A. Abramson, M.D., with a Panel Discussion. 81 pages. Seven figures. Price $2.50. St. Paul and Minneapolis: Bruce Publishing Company, 1948.

This book, an official publication of The American College of Allergists, represents the first step in the co-ordination of organizational allergy and psychodynamics. The object is to focus on the importance of emotional factors in the routine therapy of the allergic patient by both the allergist and the genera. practitioner.

Besides two articles by the author, it records the first panel discussion on the role of psychodynamics and the allergic patient, arranged by allergists unde. the auspices of The American College of Allergists at its Third Annual Meeting held in Atlantic City, New Jersey, June 8, 1947.

Amongst the invited psychiatrists attending the meeting, were Drs. O. Spurgeon English, Frank Fremont-Smith, J. A. P. Millet, Sandor Rado, and Edward Weiss. By bringing together authorities in the field of psychiatry and authorities interested in the immunologic aspects of the problem involved in treating the allergic patient, it was possible to take this first step in the consideration of the co-ordination of the disciplines of applied immunology and of psychodynamics on the same program in a constructive way. It may be mentioned that the reviewer notes that a result of this Symposium is reflected in the greater interest developed in the subject of psychodynamics by allergists.

A chapter on the psychosomatic aspects of hay fever and asthma prior to 1900, by the author is a chronologic history revealing that even in their relatively primitive therapy, our medical ancestors not only recognized the syndromes of hypersensitivity corresponding to what is now on an immunologic basis but also stressed the relationship between the psyche and allergic diseases in no uncertain way. This chapter contains many suggestions for historical exploration in the field of psychodynamics in connection with allergic syndromes.

The author's article on, "Psychodynamics and the Allergic Patient," brings forth convincing evidence of the inadequacy of the histamine theory of allergy and the importance of emotional factors. The author

feels that it is necessary to be specific in characterizing motivation by specific psychomotive forces and in other cases, neuromotive forces. The term motive force is not sufficiently specific to emphasize the primary role of the psyche which contains unmeasurable quantities. Various case records are given which classify allergic syndromes into those where immunologic factors are definitely always present and those where immunologic factors have not been proven.

The book is neatly bound in durable board, is of good paper stock and has clear illustrations. All students of allergy and psychiatry will be stimulated by this free discussion of controversial questions.

THE CASE AGAINST SOCIALIZED MEDICINE.

By Lawrence Sullivan, The Statesman Press, Washington 4, D. C., 1948 $1.50.

The author, an active journalist for thirty years brings to his subject an intimate, first-hand knowledge of governmental administration, and here presents in short chapters the historical background of Socialized Medicine. The story is told principally from the sworn testimony of witnesses before the Committees of the House and Senate. The author obviously is adverse to State Medicine and his book is not at all complimentary to those administrations who seek to promulgate centralized medicine. It will please and edify those physicians who feel as the author does.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

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CLINICAL MEDICINE

STOMACH

TOMENIUS, JOHN HILDING: *A study on gastric sediment.* (Acta Medica Scandinavica Supplementum 189, 189 pages. Stockholm, 1947).

The author has been able to show experimentally that a part of the cell remains in the gastric residuum derived from squamous cells that have been digested. It has proved that in an acid milieu squamous cells are destroyed within the course of 10 minutes, so that only nuclei and cell fragments remain. White blood corpuscles from blood proved not to be able to stand three minutes at 37° C. They became so changed that certain differentiation was rendered impossible. Leucocytes in gastric sediment were destroyed under the same conditions within the course of one minute. The nuclei in the blood corpuscles proved to be most resistant. Attempts to differentiate the nuclei of leucocytes from digested white blood corpuscles (blood) showed that only 24% of Giemsa-stained cell-remnants had the appearance of the nuclei of leucocytes. In experiments in vitro the author has been able to show that the duodenal juice exercises a strong destructive effect upon the white blood corpuscles and squamous cells in neutral or alkaline milieu. The significance of the regurgitation of the duodenal juice in this connection, on the cytological examination of gastric sediment, is pointed out. In a general survey of the importance of physiological leucopedesis for gastric sediment, it is shown that on using histamine as a stimulant and with an acid-neutralizing bicarbonate solution in the human stomach, one obtains in normal cases during fasting no leucocytes or nuclei of leucocytes in the gastric sediment.

It became evident that in order to obtain differentiable sediment one must neutralize the gastric juice in the stomach itself. The risk of the neutralizing fluid being lost through pylorus, and the acid protection thus momentarily disappearing, was avoided by supplying the fluid continuously with the help of a drip-apparatus. In order not to get the gastric residuum and earlier impurities it was necessary first of all carefully to suck up all the gastric residuum and then to wash the stomach well. Not until after these precautions was the acid neutralizing fluid/istonic (1.3%) sodium bicarbonate solution supplied through a tube to the stomach, being afterwards aspirated in 10 minute fractions. It proved that with his method one obtained a sediment that in its microscopic appearance differed entirely from what one is accustomed to find in the gastric residuum. Thus, even in cases with a normal acidity, there were to be found in the sediment differentiable cells with retained cytoplasm.

With the author's method, one found an average cell-density per visual field that considerably exceeded that of normal cases. The cellular picture was dominated by the leucocytes. These were found in several fractions in all cases within this group. In no fewer than 102 of all the 144 fractions (70.8%) definite leucocytes were found. In several of the remaining fractions it was also possible to find disintegrating cells of leucocyte size with transitional stages to quite definite leucocytes. In a good 25% of the fractions one finds eosinophile granules in the leucocytes. For comparison, one finds leucocytes in the normal material in only 1.7% of the fractions.

The second group: gastropathies with pale, atropic mucous membrane without acid secretion consisted of seven cases. Characteristic for this group was the fact that the microscopic picture of the sediment resembled that of the normal cases. One found leucocytes in altogether four of 63 fractions, i. e. 6.4%, thus rather more than in the normal cases.

In the group of duodenal ulcers and duodenal ulcer plus gastric ulcer without signs of gastritis one found the same picture as in the normal cases.

In the group of cancers of the stomach one found in the cases with corpus cancer a marked leucocytic picture. Red blood corpuscles are here also richly represented.

The case with cardia cancer showed a rich occurrence of squamous cells in all the fractions, but no leucocytes. FRANZ J. LUST

BOWEL

PENDERGRASS, R. C.: *Extrinsic deformities of the colon.* (Radiology, Sept. 1948, Vol. 51, No. 3, 320-325).

Deformity of the X-ray appearance of the colon may be produced by enlarged viscera; inflammatory processes; adhesions; endometriosis; retroperitoneal, mesenteric or omental tumors; tumors of the colonic wall; and intra-abdominal or inguinal herniae. The examination always includes a scout film of the abdomen, fluoroscopy during filling of the colon, with spot films, as indicated, films of the filled colon in various positions, and fluoroscopy and films of the colon after evacuation of the barium enema. Vaginal examination during fluoroscopy helps to separate masses in the right pelvis from the barium-distended cecum.

WELLS, J.: *The mucosal pattern of the terminal ileum in children.* (Radiology, Sept. 1948, Vol. 51, No. 3, 305-309).

The mucosal pattern of the terminal ileum in symptom-free children, as demonstrated by a barium examination, is different from that seen in most adults. The cobblestone appearance of the terminal ileum in children can be caused by aggregations of normal lymphoid tissue in the mucous membrane. This picture by itself cannot be taken as evidence of disease of the terminal ileum in children. The approximate age at which this pattern is no longer demonstrable in the normal ileum is not yet established.

GOODWIN, F. H. COLLINS, E. N.: *Diverticulosis of the colon: review of 726 consecutive cases.* (Cleveland Clinic Quart., Oct. 1948, Vol. 15, No. 4, 194-201).

Study of a large series of *uncomplicated* cases of colonic diverticulosis indicates that the symptoms resemble almost identically those of irritable colon. Diverticulosis is most commonly observed in middle-age and especially in over-weight persons. Cancer of the G. I. tract was found in 3.5 per cent of these cases and was located in the colon or rectum in the majority. Treatment is based on the prevention of future complications. The symptoms appear to be due to associated irritability of the colon rather than the diverticuli, in uncomplicated cases.

KEMP, K. H.: *Tuberculous perirectal fistula with recovery following debridement and skin grafting with simultaneous administration of streptomycin.* (J. Arkansas Med. Soc., Oct. 1948, Vol. XLV, No. 5, 101).

A case is described which presented tuberculous sinus involvement of the skin about the anus and was rapidly and efficiently cured by skin grafting and simultaneous therapy with streptomycin, whereas the same process previously had spread with simple surgical care consisting of debridement and dressings. It was noted that this case of tuberculous sinus infection showed a tendency to aggravation during each menstrual period.

ROSE, T. F.: *Mesenteric chylangioma in a nine months old baby.* (Med. J. Australia, July 31, 1948, 124-126).

The author reports a case of mesenteric chylangioma *(chylangioma cavernosum)* in a child, aged nine months, associated with infection and commencing intestinal obstruction. The diagnosis was not made prior to operation, an appendiceal abscess being simulated. The tumor was removed together with four inches of ileum. Recovery was uneventful and a follow-up examination disclosed no further trouble. This particular type of mesenteric lymphangioma is excessively rare, only seven cases having been previously reported. The tumor was approximately five cms. long.

ULCER

BLIXENKRONE-MOLLER, N.: *Vagotomy in the treatment of peptic ulcer.* (Nordisk Med., Sept. 10, 1948, Vol. 39, No. 37, 1629-1635).

The author surveys our present knowledge of vagotomy in the treatment of peptic ulcer and records eight cases. He favors vagotomy where gastro-enterostomy or gastric resection has been employed but cannot recommend the routine use of vagotomy in peptic ulcer until further information has accumulated with respect to late results and possible late sequelae.

HIRSCHBERG, F.: *Importance of symptomatology in the X-ray diagnosis of gastric ulcer.* (Nordisk Med., Sept. 17, 1948, Vol. 39, No. 38, 1663-1664).

This article is a statement by a roentgenologist that the symptoms of dyspepsia upon which formerly the diagnosis of gastric ulcer depended before it was possible to demonstrate craters and niches, ought still to influence the diagnosis of ulcer, despite the roentgen findings.

Clinical Experience With A New Modified Protamine Insulin (NPH-50)

By

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and

ALEXANDER MARBLE, M.D.

BOSTON, MASS.

THE INTRODUCTION OF protamine zinc insulin in 1937 marked a notable advance in the treatment of diabetes. Up until that time "regular" or "plain" insulin had been the only type available. Although this unmodified insulin had revolutionized the outlook for diabetic patients in general, allowing them longer and more useful lives, its short duration of action was a disadvantage. Even with the use of three or four doses daily it was impossible for many patients with severe diabetes to avoid a marked rise in the blood sugar after midnight unless with inconvenience a dose was taken not only at bedtime but also at about 2 A. M. The result was that in juvenile patients and others with this type of diabetes, high fasting blood sugar values were the rule and one was forced to admit that the diabetes was inadequately controlled for at least one-fourth of each day. Protamine zinc insulin changed this and when given daily before breakfast allowed in most patients a normal fasting blood sugar with concomitant betterment of general health and disappearance of complications such as retardation of growth and development and hepatomegaly in juvenile cases.

It has been the general experience, however, that in most children and in other patients with severe diabetes, daytime hyperglycemia and glycosuria cannot be well controlled with protamine zinc insulin alone. Consequently, the practice early was adopted of the use of unmodified insulin given at the same time in the morning before breakfast. Since this involved two injections, attempts have been made to combine the slowly acting and rapidly acting varieties by mixture either in the syringe or in the bottle. Much work has been done along this line and it is generally conceded that with most patients a mixture of two parts of unmodified and one part of protamine zinc insulin is the one which is the most suited. There has not been general agreement, however, that insulin mixtures provide as meticulous control of diabetes as if the two varieties are given by separate injection.

Within the last few years modified forms of protamine insulin have been introduced. MacBryde (1) has reported upon the use of such an insulin, prepared by Eli Lilly and Company and designated as "NP-50." This product has the disadvantage of not being stable for long periods of time. Still more recently Krayenbühl and Rosenberg (2) in Hagedorn's laboratory announced the production of protamine insulin in crystalline form. As reported by Peck (3) in 1946, this new modified protamine insulin has been prepared by Eli Lilly and Company according to the method of Hagedorn whereby the amount of protamine used per 100 units of insulin is 0.50 mg. in contrast to 1.25 mg. in the market protamine zinc insulin. The new modified protamine insulin has been designated as NPH-50; "N" refers to the neutral reaction (PH 7.2), "P" to protamine, "H" to Hagedorn and 50 to the content of protamine. The amount of zinc is quite small. NPH-50 is identical with NPC-50 insulin described by Peck (3). NPH-50 insulin has an effect somewhat shorter than that of market protamine zinc insulin and is considerably more rapid in onset of action. Having had the opportunity during the summer of 1948 to use this new type of insulin with boys at the Elliott P. Joslin Camp at Charlton, Massachusetts, we now report the results of these studies.

CLINICAL MATERIAL AND METHODS

During the eight weeks of the camp season 116 boys were cared for of whom 115 received insulin. Of these, 94 were given the NPH-50 type for a sufficient period of time to evaluate its activity. The boys ranged in age from 3.3 to 16.3 years and in duration of diabetes from 0.3 to 12.4 years. In most instances the diabetes was of severe grade; the average total dose of insulin taken at home prior to entrance to the camp was 12 units of crystalline and 26 units of protamine zinc insulin, a total of 38 units daily. A summary regarding the ages of the subjects, duration of diabetes, insulin dose and diet is given in Table I.

The camp was operated as any other summer camp for children, being located in a wooded tract on a small lake some 50 miles from Boston. The children were housed in cabins each accommodating eight campers and two counsellors. Meals were served in a common dining hall and here all food was accurately weighed using gram scales. The total quantity of urine was saved daily and tested for diacetic acid and sugar and the percentage of sugar, if any, was determined quantitatively by the Exton modification (4) of the Sumner (5) method adapted for use with the photoelectric colorimeter. In addition, single specimens of urine were obtained at 7:15 and 11:15 A. M. and at 4:15 and 8:00 P. M. and tested qualitatively for sugar by Benedict's method. To eliminate, in so far as possible, the confusion often arising from "overflow" glycosuria," campers voided at 7:00

From the George F. Baker Clinic, Elliott P. Joslin, M.D., Medical Director, New England Deaconess Hospital, Boston, Massachusetts.

and 10:15 A. M. and at 2:15 and 7:00 P. M.

Twice weekly capillary blood sugar determinations were made in each case; with half the campers this was done on Monday and Thursday and with the other half on Tuesday and Friday. Blood was drawn from an ear lobe at 7:15 and 11:15 A. M. and at 4:15 and 8:00 P. M. Determinations of sugar content were made by Folin's method (6) adapted for use with a photoelectric colorimeter. A well equipped laboratory was housed in one of the buildings in which facilities were available for studies under conditions which approximated those of a hospital laboratory. Three technicians were in constant attendance.

Activities resembled those of the usual summer camp with both active and relatively inactive periods in the forenoon, afternoon and evening. It had been anticipated that physical exercise would markedly influence the blood sugar and urine tests and such proved to be the case. It was customary to find that with increase in activity marked reductions were possible in the total insulin dosage, even though increases in the diet were allowed.

Insulin was administered daily 30 to 45 minutes before breakfast by one of the two graduate nurses on duty.

In addition to the three main meals, feedings were given in the mid-morning and mid-afternoon and at bedtime. Variations were introduced in the amount or frequency of such feedings depending upon the type of insulin under study and the activity program of the campers, but in all instances the total diet for the day was kept constant.

PLAN OF STUDY

Almost without exception patients reporting to camp had been on a regime which included two injections of insulin before breakfast, one of unmodified and a second of protamine zinc insulin. Six campers had been receiving protamine zinc insulin alone, one globin insulin, three insulin mixtures, two NPH-50, and one NP-50. It was early apparent, both from questioning and upon preliminary tests, that the average patient had not been well controlled at home and in most instances the prescribed diet had been greatly exceeded. Consequently, seven to 10 days were allowed for stabilization and regulation on a weighed diet, regular physical activity and insulin schedule which included the unmodified and protamine zinc insulin given by separate injection before breakfast. Following this initial period, campers were then shifted to NPH-50 and kept on this variety for four to 14 days with an average of six to 10 days per camper. In those campers whose stay at camp was long enough, a return was made to the unmodified-protamine zinc insulin combination and then later back to NPH-50. In this way there were 34 campers with whom at least two periods of observation with both regimes were possible. In certain patients a trial period with globin insulin with zinc was carried out in order to compare the general effect and length of action of this variety of insulin with both NPH-50 and

TABLE I

Summary of Data Regarding 79 Campers Discharged on NPH-50 Insulin

Age Group Years	Number Campers	Duration Diabetes Years	Insulin On Admission CI	Insulin On Admission PZI	Insulin On Admission Total	Insulin At Discharge NPH-50	Diet On Admission C	Diet On Admission P	Diet On Admission F	Diet On Admission Cal.	Diet At Discharge C	Diet At Discharge P	Diet At Discharge F	Diet At Discharge Cal.
			Units			Units	Grams				Grams			
3 - 4.9	5	1.8	8	13	21	20	155	69	78	1598	165	78	81	1701
5 - 7.9	12	3.4	7	15	22	22	164	78	85	1733	185	89	92	1924
8 - 9.9	11	3.7	11	18	29	24	180	83	82	1790	193	94	99	2039
10-11.9	20	4.9	13	25	38	36	202	101	102	2130	215	116	112	2332
12-13.9	18	4.7	16	32	48	36	206	109	109	2241	220	126	124	2500
14-16.3	13	4.7	18	34	52	36	215	108	108	2264	235	133	125	2597

TABLE II

INSULIN PROGRAMS USED IN STUDY

PROGRAM NUMBER	I	II	III	IV	V
TYPE OF INSULIN	CI + PZI	CI + PZI → NPH50	CI + PZI → NPH50 → CI + Gl.	CI + PZI → CI NPH50 mixed → NPH50	CI + PZI → CI + Gl. → NPH50 → CI NPH50 mixed
CAMPER-DAYS, TOTAL NUMBER	261	950 / 1149	186 / 124 / 88	47 / 8 / 71	69 / 32 / 82 / 13
CAMPERS, NUMBER	20	78	10	4	3

CI + PZI = Crystalline plus protamine zinc insulin given daily before breakfast by separate injection
NPH-50 = New modified protamine insulin given in a single dose daily before breakfast with zinc
CI + Gl. = Crystalline plus globin insulin given daily before breakfast by separate injection

the unmodified protamine zinc insulin combination.

Since the primary objective was the operation of a successful summer camp and only secondarily the study of new insulins, it was necessary to change the doses of insulin from time to time depending upon the behavior of the blood sugar and urine tests. Consequently, it was not possible to observe for any appreciable length of time the effect of exactly comparable doses of the different varieties of insulin. However, this seems a minor disadvantage in view of the fact that regardless of the type of insulin being employed the aim throughout was, in so far as possible, to maintain a satisfactory blood sugar and as little glycosuria as possible and yet avoid frequent hypoglycemic reactions.

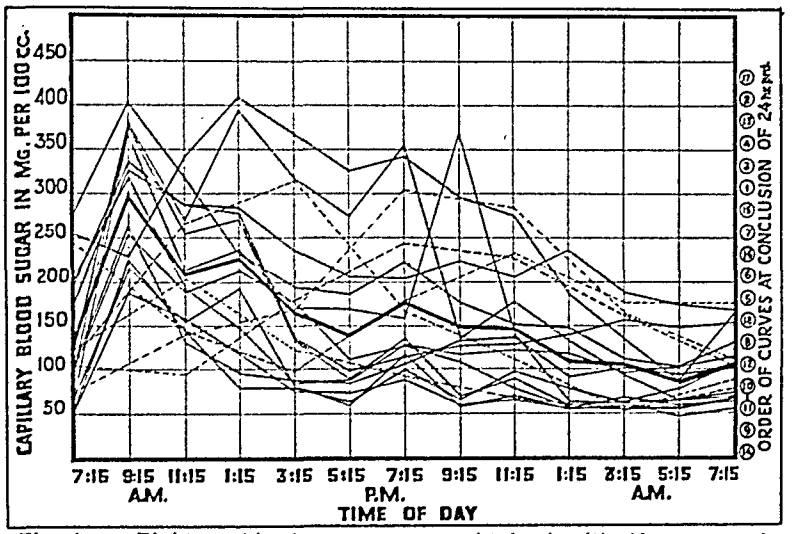


Fig. 1. — Eighteen blood sugar curves obtained with 10 campers by determinations made at 2 or 4 hourly intervals throughout 24 hours while the subjects were maintained on their usual regime of diet and activity.
It is obvious that blood sugar values at 9:15 A. M. were in general quite high but it must be remembered that this was only one hour after finishing breakfast, a time which is rarely selected for the determination of the blood sugar with patients on any insulin regime. By 11:15 A. M. values had fallen to within an acceptable range.

RESULTS

Blood Sugar Curves over 24 Hours: In an attempt to ascertain the behavior of the blood sugar throughout an entire day and to determine the length of action of NPH-50, a group of 10 campers was selected with which capillary blood sugar determinations were carried out at frequent intervals over a period of 24 hours. Five campers had blood sugar determinations every two hours while the other five had such tests every four hours. Approximately 10 days later eight of the campers who had been in the previous group had blood sugar tests every two hours. During this time the normal camp life of the boy was not disturbed except for the brief time required for the collection of blood and the obtaining of urine specimens. Technicians visited the cabins of the campers during the night and usually sleep was disturbed very little. In Figure 1 are shown the 18 curves obtained with the 10 boys. It will be noted that the fasting blood sugar in most instances ranged from 55 to 100 mg. per 100 cc. with a concentration of points between 100 and 125 mg. With the taking of breakfast, blood sugar values rose sharply to the highest point in the day so that at 9:15 A. M. values ranged from 185 to 400 mg. per 100 cc. Following this there was considerable variation in the individual results obtained, but in general the blood sugar fell during the course of the waking part of the day and then maintained a fairly steady level from 11:15 P. M. to 5:15 A. M. Most values during the night ranged between 55 and 150 mg. per 100 cc. It is noteworthy that there was a very slight tendency for the blood sugar at 7:15 A. M. to be higher than that at 5:15 A. M., suggesting that the main force of action of the insulin had been spent.

The broad heavy line in Figure 1. is a composite curve obtained by averaging values for the various time intervals. In Figure 2. are shown the 11 curves which conform to the general pattern of the composite curve. In so far as it is possible to make a statement on the basis of available data, the curves in Figure 2. and the composite curve in Figure 1. represent the behavior of the blood sugar of a patient receiving NPH-50 in reasonably adequate dosage while that patient is physically active and receiving his usual meals and between meal lunches.

Results of Maintenance Studies: The amount of data available regarding the day-by-day experience with NPH-50 as contrasted with the unmodified-protamine zinc insulin regime is so great as to make summarizing difficult. However, in Figures 3, 4, 5, and 6 are given representative charts showing the comparisons of the results obtained with the two insulin programs. It is obvious that satisfactory control is possible with both programs and that with care as to regulation of insulin dosage and uniformity of diet and physical activity, satisfactory blood sugar values and minimal glycosuria are possible.

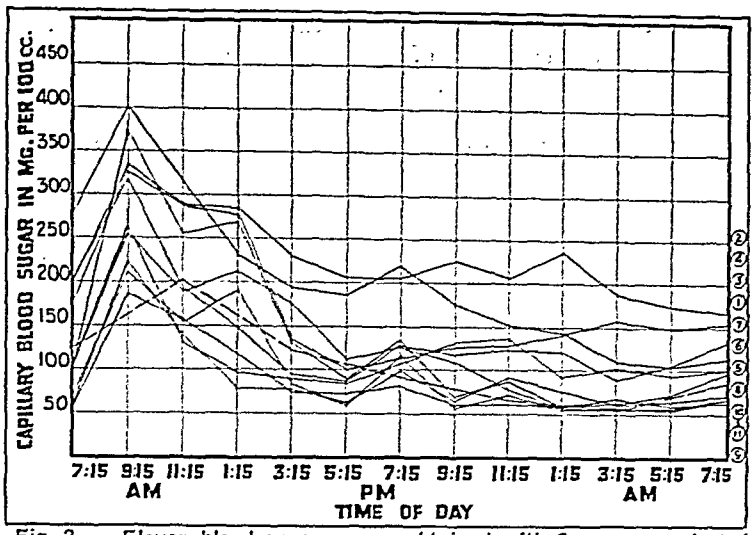


Fig. 2. — Eleven blood sugar curves obtained with 8 campers selected from the curves shown in Figure 1, in order to illustrate the most common trend following a single dose of NPH-50 insulin given in the morning before breakfast. On the day of the test the campers followed their usual routine of activity and meals.

It is evident that hypoglycemic levels of blood sugar were obtained with both NPH-50 and the unmodified-protamine zinc insulin combination. Certain facts seem warranted from a study of these figures and from the large number of similar charts not reported here: (1) In general, as good control is possible with NPH-50 given in a single dose daily as with two separate injections of unmodified and protamine zinc insulin; (2) There are exceptions but in general the effective dose of NPH-50 is appreciably lower than the total dose of unmodified and protamine zinc insulin on the other program; (3) The somewhat increased rapidity of action of NPH-50 as compared with market protamine zinc insulin is evident from the fact that lower blood sugar values, even to the point of hypoglycemia, occur as early as the latter part of the afternoon; whereas, with market protamine zinc insulin, reactions occurred most commonly during the night or early morning hours. However, the effect of NPH-50 continues for well over twenty-four hours and probably for 28 to 30 hours as shown by hypoglycemic reactions in some patients in the latter part of the forenoon. With NPH-50 as with market protamine zinc insulin, early morning reactions may occur.

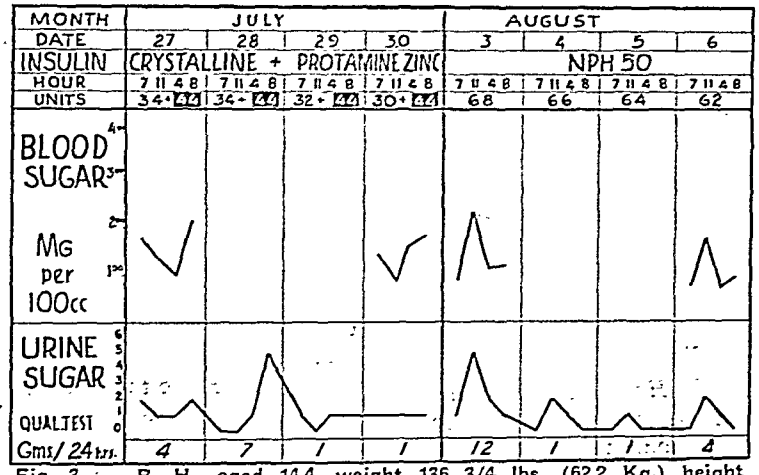


Fig. 3. — R. H., aged 14.4, weight 136 3/4 lbs. (62.2 Kg.) height 66 1/4 inches (175 cm.) without shoes, with diabetes of 3.0 years' duration. Diet: Carbohydrate 226 Gm., Protein 117 Gm., and Fat 114 Gm., a total of 2,398 calories. This chart shows a comparison of blood sugar curves and amount of sugar in the urine for four consecutive days on each of the two insulin regimes under study. Unmodified and protamine zinc insulin were given by separate injection each morning before breakfast.
In this and similar charts the qualitative tests for sugar in the urine were plotted according to the following scale: O, no sugar; 1, green with Benedict's test; 2, green-yellow; 3, yellow-green; 4, yellow; 5, orange or brown; 6, red.

It must be emphasized that the blood sugar trends of some patients did not conform to the average pattern. Consequently, although the response to NPH-50 can in most instances be predicted, only trial with the individual patient can be taken as a safe guide

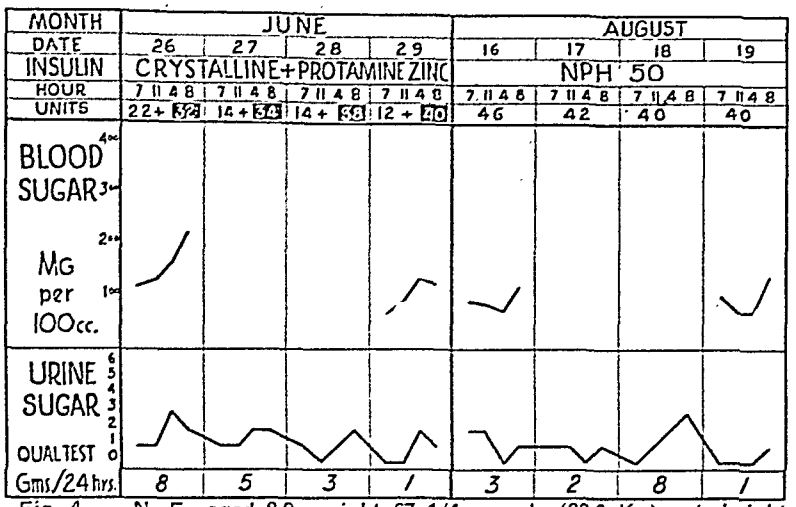


Fig. 4. — N. F., aged 9.9, weight 67 1/4 pounds (30.6 Kg) net, height 53 1/2 inches (137 cm.) without shoes, with diabetes of 4.8 years' duration. Diet: Carbohydrate 183 Gm., Protein 83 Gm., and Fat 91 Gm., a total of 1,883 calories.

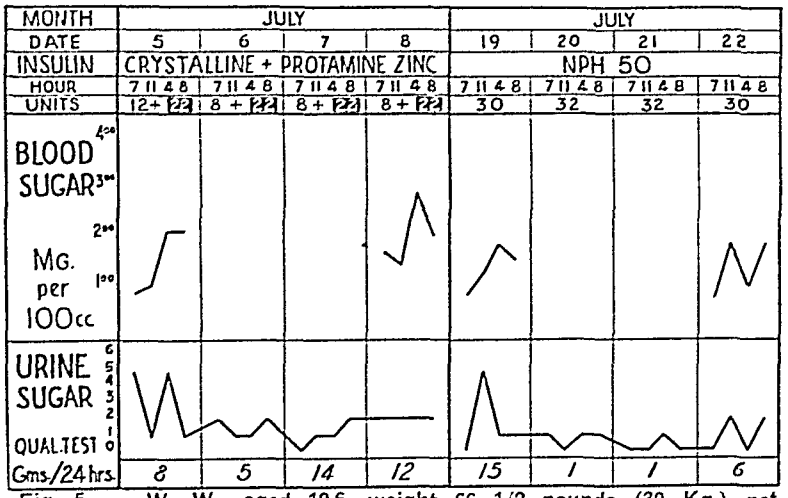


Fig. 5. — W. W., aged 10.6, weight 66 1/2 pounds (30 Kg.) net, height 55 inches (141 cm.) without shoes, with diabetes of 1.2 years, duration. Diet: Carbohydrate 247 Gm., Protein 108 Gm., and Fat 113 Gm., a total of 2,437 calories.

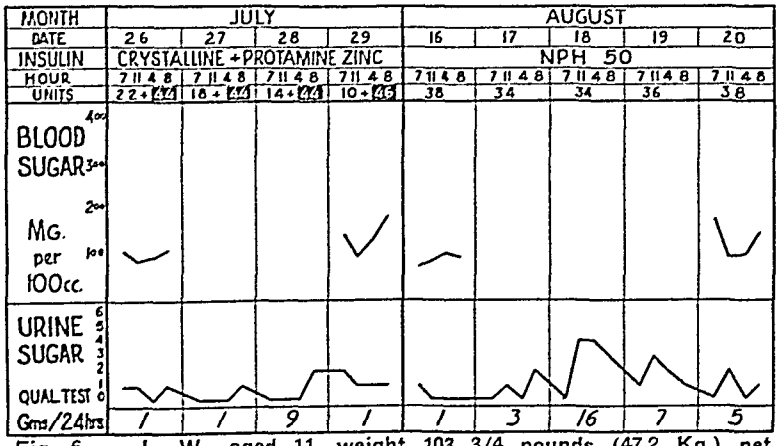


Fig. 6. — L. W., aged 11, weight 103 3/4 pounds (47.2 Kg.) net, height 59 1/4 inches (152 cm.) without shoes, with diabetes of 2.4 years' duration. Diet: Carbohydrate 284 Gm., Protein 118 Gm., and Fat 111 Gm., a total of 2,287 calories.

SPECIAL FEATURES IN USE OF NPH-50

To call attention to the difficulties encountered in the use of NPH-50 Figures 7. and 8. have been prepared. In Figure 7. is illustrated the fact that with some patients that dose of NPH-50 which will provide a normal or slightly sub-normal fasting blood sugar may still allow well-marked hyperglycemia in the forenoon following breakfast together with considerable glycosuria.

talline characteristics, the tendency for adsorption of unmodified insulin is much less than with market protamine zinc insulin and hence mixtures in the syringe can be made and still preserve a large share of the quick action of the unmodified insulin added. Actually, in our experience at camp it was found that the addition of even a small dose of unmodified insulin, such as four to six units, often had a marked hypoglycemic effect. Later experience has shown,

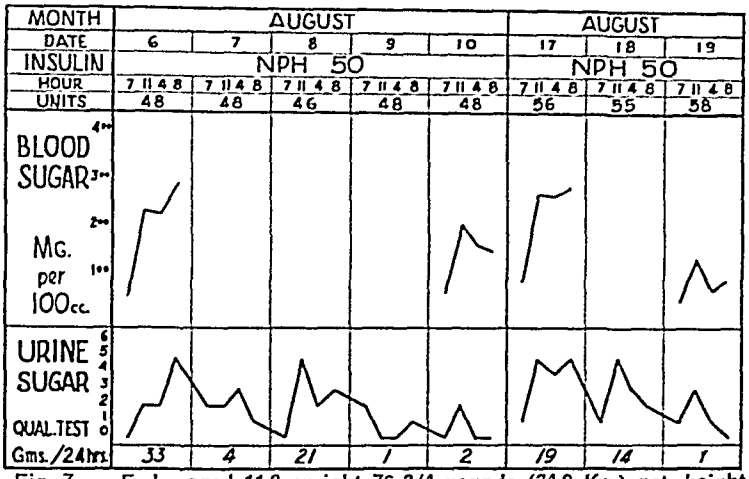


Fig. 7. — E. L., aged 11.8, weight 76 3/4 pounds (34.8 Kg.) net, height 55 1/4 inches (142 cm.) without shoes, with diabetes of 8.5 years' duration. Diet: Carbohydrate 214 Gm., Protein 116 Gm., and Fat 112 Gm., a total of 2,328 calories.

Note that the fasting blood sugar was unusually low being even at hypoglycemic levels. Yet during the rest of the waking part of the day there was hyperglycemia and glycosuria which was in some instances quite marked. Experience showed that could be corrected by shifting carbohydrate from breakfast (and even lunch if necessary) to the bedtime lunch, or by the lowering of the dose of NPH-50 insulin and mixing directly in the syringe a small dose of unmodified insulin.

With such patients the hyperglycemia may be prevented by decreasing the amount of carbohydrate given at breakfast and transferring this food to the bedtime feeding. If this is not possible, an alternative is to add a small dose of unmodified insulin to the dose of NPH-50 in the syringe. Fortunately, with NPH-50, because of its predominately crys-

however, that in certain situations much larger doses may be used. For example, in a patient recently treated in the hospital, 24 units of regular insulin were mixed in a syringe with 90 units of NPH-50.

Another difficulty is that of the marked hypoglycemic tendency during the night. This can be overcome by giving a bedtime lunch which contains

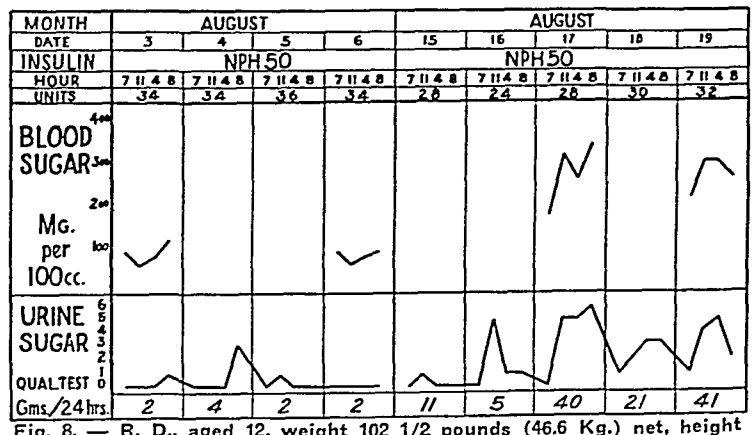


Fig. 8. — R. D., aged 12, weight 102 1/2 pounds (46.6 Kg.) net, height 60 1/2 inches (155 cm.) without shoes, with diabetes of 1.4 years' duration. Diet: Carbohydrate 220 Gm., Protein 131 Gm., and Fat 125 Gm., a total of 2,529 calories.

During the first 4 days illustrated the camper was physically very active, participating in the camp program. During the last 5 days illustrated he was inactive because of personal behavior and because of participation in a relatively quiet program during the last week of camp. The effect on the control of diabetes is evident.

as much as 30 to 40 grams of carbohydrate in addition to more slowly absorbed protein and fat.

It was early found that variations both in diet and in amount of physical activity affected greatly the degree of control of diabetes with NPH-50 as with any type of insulin. In Figure 8. is shown the increase in hyperglycemia and glycosuria which in one camper accompanied days of relative inactivity.

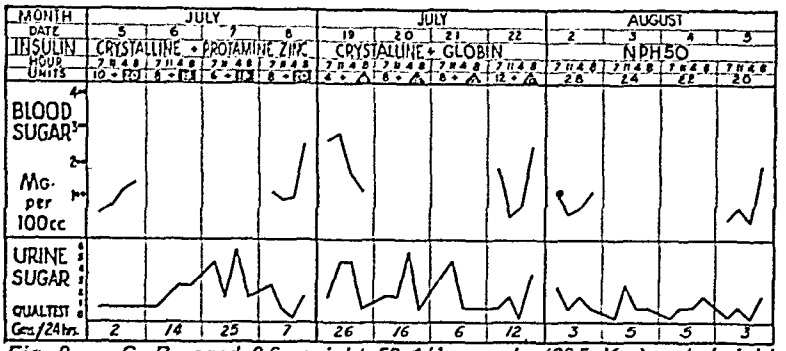


Fig. 9. — G. P., aged 9.6, weight 58 1/4 pounds (26.5 Kg.) net, height 48 1/4 inches (124 cm.) without shoes, with diabetes of 5.9 years' duration. Diet: Carbohydrate 197 Gm., Protein 94 Gm., and Fat 87 Gm., a total of 1,947 calories.

It appears evident from this chart that the control of hyperglycemia and glycosuria was appreciably better on a single dose of NPH-50 insulin before breakfast as compared with combinations of either crystalline and protamine zinc insulin or of crystalline and globin insulin with zinc. The relatively high fasting blood sugar values during the days which crystalline and globin insulin with zinc were given are noteworthy.

PRESENTATION OF DATA IN DETAIL

There were 34 campers in whom it was possible to make a comparison in two separate periods of the effect of NPH-50 on one hand and of the crystalline-protamine zinc insulin combination on the other. The data obtained in these cross-over studies have been summarized in a table which because of lack of space, is not reproduced here. Study of the table shows considerable variations in results as might be anticipated. However, close scrutiny of the days during which NPH-50 insulin was used reveals that in general a single dose of this variety of insulin provided as good or better control of hyperglycemia and glycosuria as the double injection of the crystalline and protamine zinc insulin variety.

GLOBIN INSULIN WITH ZINC

Opportunity was afforded in 13 patients for comparing the effect of NPH-50 and the unmodified-protamine zinc insulin combination with a program in which unmodified and globin insulin with zinc were given in the morning before breakfast by separate injection. From this group Figures 9. and 10. have been selected to serve as examples of the type of results obtained. Although with certain of these 13 patients satisfactory control was obtained on the unmodified-globin insulin with zinc program, in general the results were not impressive. One disadvantage was a tendency to hypoglycemic reactions in the afternoon. This could be prevented by the use of more liberal afternoon feedings. A second and more serious disadvantage was the failure in these patients with severe diabetes for the effect of globin insulin with zinc to carry through a full 24 hours. The result was that often the fasting blood sugar was considerably

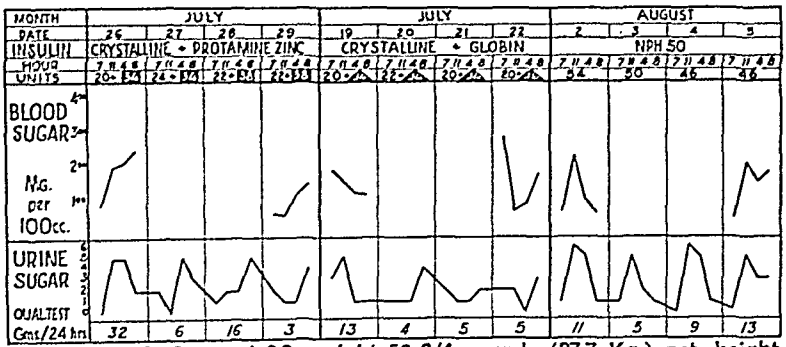


Fig. 10. — C. S., aged 6.2, weight 56 3/4 pounds (27.7 Kg.) net, height 49 inches (125) cm.) without shoes, with diabetes of 2.6 years' duration. Diet: Carbohydrate 171 Gm., Protein 121 Gm., and Fat 110 Gm., a total of 2,158 calories.

It is evident that as good control of diabetes was obtained with a single dose of NPH-50 insulin as with the combination of either crystalline and protamine zinc insulin or of crystalline and globin insulin with zinc. Particularly noteworthy is the relatively high fasting blood sugar values obtained when globin insulin with zinc was given in contrast with normal or below-normal values on the other programs. The four days on NPH-50 insulin illustrates the rise in blood sugar at 11:00 A. M. as encountered with certain other patients. This also responded to shifting carbohydrate from breakfast to the bedtime feeding.

elevated. The impression seems well-founded that NPH-50 has a duration of effect appreciably longer than that of globin insulin with zinc and this somewhat greater length of action is a decided advantage in patients with severe diabetes.

Hypoglycemic Reactions Due to Insulin

As has been stated earlier a definite attempt was made throughout the camp season to control the diabetic condition carefully, keeping blood sugar values as nearly normal as possible and reducing glycosuria to a *minimum*. With this in mind and in view of the strenuous character of the physical activity at camp it is not surprising that insulin reactions were fairly common with all types of insulin used. In studying Table III in which insulin reactions are tabulated, it must be kept in mind that the diagnosis of such was made on clinical grounds in most instances since with the boys engaging in play it was manifestly impossible to secure determinations of the blood sugar in every instance. An insulin reaction was classified as such if a camper complained of weakness, hunger, headache or any of the other well-known symptoms of hypoglycemia and if his condition was judged by the physician, nurse or trained counsellor to be compatible with such. Mild reactions were treated by giving at once a wafer containing two grams of dextrose and repeating the dose, if necessary, one or more times. More severe reactions were treated by giving 50 to 100 grams of ginger ale or orange juice repeating this amount if the situation warranted. Reactions during which the patient was unconscious or uncooperative were treated with the intravenous injection of 20 cc. of 50 per cent dextrose in a sterile buffered solution. At times 0.3 cc. of adrenalin was administered subcutaneously. The number of reactions listed in Table III errs if anything on the side of being too liberal since in order to keep the camper at his activity, signs and symptoms of reactions were noted as soon as possible and treated without delay.

TABLE III

Incidence of Reactions With Various Insulins

Type of Insulin	CI + PZI	NPH-50	CI + Gl.	CI + (mixed) NPH-50
Camper-Days, Total Number	1513	1396	120	21
Reactions, Number	273	320	41	14
Incidence, Per Cent	18	22.9	34.1	66.6

Total camper-days of insulin — 3050
Toal number of reactions — 648
Incidence, per cent — 21.2

CI equals Crystalline Insulin
PZI equals Protamine zinc insulin
Gl. equals Globin insulin with zinc

In all, 273 reactions were observed in 1,513 camper-days during which a combination of unmodified and protamine zinc insulin was given. Three hundred twenty reactions occurred on 1,396 camper-days during which NPH-50 insulin was given. Forty-one reactions occurred on 120 days when a combination of unmodified and globin insulin was given. When unmodified and NPH-50 were mixed in the syringe 14 reactions occurred on 21 camper-days. The incidence of reactions per Camper days in the four groups was therefore 18 per cent, 22.9 per cent, 34.1 per cent and 66.6 per cent respectively. The high incidence of reactions noted with the unmodified -NPH-50 mixture cannot be considered significant in view of the small number of patients so treated and the investigational character of this part of the study.

As has been mentioned previously, the most common time of reactions with patients receiving both modified and market protamine zinc insulin was in the late forenoon and in the early morning hours. The most common time for reactions in patients receiving NPH-50 was in the latter part of the afternoon and in the early morning hours. Reactions in patients receiving globin insulin occurred usually in the mid- and late afternoon.

Follow-Up Studies

The experience in camp showed quite well that under the conditions of the study a single injection of NPH-50 insulin controlled the condition of most severe juvenile diabetics as well, or better, than did the combination of unmodified and protamine zinc insulin given by separate injection. However, it must be admitted that the conditions of study in many respects approached the ideal and provided for carefully weighed diets, close laboratory evaluation, supervision of physical exercise and the opportunity for frequent adjustment of diet and insulin dose. Such conditions are difficult to provide for the juvenile patient under home conditions. Consequently, the follow-up of such patients after discharge from camp seemed a most important matter.

An attempt was made to do this by means of visits of the patients to the physician's office and by questionnaires sent to the patients and their families. One such questionnaire was sent out approximately two weeks after the close of the camp season at a time when the boys had been on NPH-50 for from four to eight weeks. Of 79 campers to whom the questionnaire was sent, answers were received from 58. With one exception all had continued taking the NPH-50 insulin in a single dose before breakfast. Nineteen had found it necessary to supplement this with occasional doses of regular or crystalline insulin and 28 had found that the basic dose of NPH-50 needed to be increased under home conditions. However, the increase in dose had not been large as shown by the fact the average dose taken at the time of the questionnaire was 34 units in comparison with an average of 29 units at the time of discharge from camp. Fifty-one campers stated that they had been following their diet at home, but direct information on this point is lacking. Four patients were admittedly breaking their diet and this common ten-

dency as well as variations in physical activity at home invalidate to a considerable degree any conclusions drawn from a comparison of insulin preparations under home conditions. Many patients had found that a sizable bedtime lunch was desirable to prevent night-time reactions. Thirty-seven of the 58 patients reported that the urine tests before breakfast were usually blue or green with Benedict's solution. At least 32 reported that the tests before the evening meal and at bedtime were satisfactory. In most instances the tests before the noon meal showed some sugar. Twenty reported that insulin reactions had been less frequent than under the former regime. Only one severe reaction (with convulsions) requiring adrenalin was reported. In only one instance were reactions troublesome enough to cause the patient to give up NPH-50 insulin and return to the former program. Reactions occurred most frequently in late afternoon, evening and early morning hours. With only two exceptions, patients stated that they liked the new insulin, but it must be confessed that the chief reason given by most was the fact that a single injection daily was required. Twelve patients or their parents believed that from the standpoint of control of the diabetes, the NPH-50 was no better than that of the combination of unmodified and protamine zinc insulin.

All in all, the experience with NPH-50 insulin under home conditions has been favorable provided due allowance is made for variations in diet and physical activity, handicaps which cannot be overcome by any of the known insulin preparations. It must be reemphasized that, as with any insulin, the response of the patient is an individual matter and cannot be predicted with complete accuracy. Rearrangement of the diet has solved certain of the difficulties encountered with the NPH-50 insulin. With most patients the amount of carbohydrate at breakfast can to advantage be reduced and the mid-morning lunch omitted. The giving of 10 grams of carbohydrate in the mid-afternoon is advisable with a sizable bedtime lunch consisting often of four crackers (2 1/2 inches square), 240 grams of milk and 30 grams of cheese. By this arrangement hyperglycemia and glycosuria can be lessened during the forenoon and insulin reactions prevented in the late afternoon, evening and night.

SUMMARY

1. Studies are reported with the use of a new modified protamine insulin (NPH-50 — Lilly) used with 94 boys with severe diabetes ranging in age from 3.3 to 16.3 years and in duration of diabetes from 0.3 to 12.4 years. The studies were carried out in a summer camp in which conditions of diet and activity could be well controlled.

2. When compared under similar conditions of diet and exercise it was found that a single dose of NPH-50 insulin provided as good or better control of hyperglycemia and glycosuria as did a combination of unmodified and protamine zinc insulin given by separate injection in the morning before breakfast.

3. Studies indicated a more rapid onset and somewhat shorter duration of action of NPH-50 when compared with the market variety of protamine zinc insulin. Blood sugar determinations carried out at two to four hourly intervals during a 24-hour period indicated that NPH-50 insulin exerts an effect for at least a full 24 hours and probably for 28 to 30 hours. Its maximum effect begins in the late afternoon and extends into the evening and night. By diminution of carbohydrate at breakfast and during the forenoon and by the giving of an afternoon lunch and a sizeable bedtime lunch hypoglycemic reactions can be prevented.

4. Follow-up studies after camp discharge have in general indicated favorable results and suggest that good control of diabetes can be secured under home conditions provided reasonably constant conditions of diet and physical activity are maintained. The advantage of a single injection daily appeals to patients and for the most part the insulin has been popular with both parents and patients.

5. In the course of the study the effect of giving unmodified and globin insulin with zinc by separate injection in the morning before breakfast was compared in 13 patients with a single injection of NPH-50 and with a combination of unmodified and protamine zinc insulin given by separate injection. The results indicated a tendency to hypoglycemia in the afternoon when globin insulin was given. This was overcome with the use of afternoon feedings but a more serious disadvantage was the failure in patients with severe diabetes for globin insulin to exert an effect for a full 24 hours with the result that the fasting blood sugar was often considerably elevated.

ADDENDUM

Note added May 15, 1949: Since the preparation of the above, the patients concerned have been kept under observation both by means of office and hospital visits and by letter. A recent survey has yielded in general the same findings as before, namely, that under home conditions as good or better control may be attained with NPH-50 as with market protamine zinc insulin. However, the results again point to the fact that it is difficult to evaluate any type of insulin with juvenile patients at home because of the difficulty encountered in maintaining constant conditions of diet and activity. Of 65 boys answering a recent questionnaire, all but four had continued with NPH-50 insulin. Thirty of the 65 were taking supplementary doses of unmodified insulin either daily or at times of increased glycosuria. Reactions apparently had been no more common than with other treatment programs. The total insulin dose of 60 boys from whom data were available was 44 units at the time of the survey as compared with 31 units at the time of discharge from camp.

Recently 10 adult patients aged 40 to 78 years with duration of diabetes from one to 23 years were studied under hospital conditions. The range of the insulin dose was from 20 to 76 units daily. Urine and blood sugar tests were determined during a control period of one or more weeks during which protamine zinc insulin alone or in combination with unmodified insulin was used. Then a period of three to eight days on NPH-50 insulin was instituted. Finally the patients were returned to the previous schedule with unmodified and protamine zinc insulin. Space does not permit giving detailed data but it was evident that with such patients NPH-50

insulin can be used without difficulty to replace either protamine zinc insulin alone or this insulin plus unmodified insulin. When NPH-50 is used to replace the combination of the two market types, its dose is usually quite close to the sum of the doses of the other two varities.

In the earlier experience with NPH-50 insulin (but not appreciably in the camp studies), some difficulty was encountered in securing a uniform suspension with certain lots due to clumping of the precipitate in the bottle. However, this problem of the physical characteristics of the preparation has apparently been solved by the manufacturers since with lots now received a uniform suspension is easily obtained by gentle mixing of the contents of the vial.

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Diagnostic Difficulties In Rectosigmoid Lesions

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THE DIFFERENTIAL DIAGNOSIS of recto-sigmoid lesions is often quite difficult. Even after a careful history, physical examination, digital rectal examination with the "educated finger," proctosigmoidoscopy and roentgenological study, the exact nature of the lesion may still be in doubt.

The symptoms of rectal and recto-sigmoid lesions are well known and the early manifestations have recently been repeatedly reemphasized. Swinton and Gillespie (1) have grouped them under the following headings: (A) Any abnormality of the stool including the presence of blood, pus or mucus, or any change in the caliber of the stool. (B) Any change in the normal bowel habit of an individual including variations of constipation and diarrhea. (C) Any unexplained abdominal pain, cramps, indigestion, feeling of fullness or rectal tenesmus. (D) Any unexplained abdominal tumor or anemia.

Lesions of the recto-sigmoid may be either intrinsic or extrinsic. They may be neoplastic, inflammatory, or functional.

Intrinsic lesions include: (a) neoplastic; benign tumors, polyps, carcinoma, sarcoma. (b) Inflammatory: hyper-plastic tuberculosis, non-specific granulomas, syphilis, segmental ulcerative colitis, diverticulitis, congenital and acquired strictures. (c) Functional; spastic colitis and megacolon.

Extrinsic lesions have been listed as follows (Marshak (2) (a) Tumors: ovarian cysts, fibroids, retroperitoneal tumors, lymphosarcoma, ovarian carcinoma, metastatic carcinoma. (b) Inflammatory manifestations: pelvic inflammatory disease, the effects of irradiation therapy, sigmoiditis, post-operative adhesions, carcinoma of the cervix with frozen pelvis, endometriosis and, one can add, perisigmoid reaction following perforation by foreign bodies, (Meltzer 3) and high perirectal abscess.

Regarding the frequency of the above different lesions causing extra-rectal masses; there have been two studies of which we are aware, Brust (4) and Buie (5). Both found pelvic inflammatory disease responsible for extra-rectal masses in nine and 10 per cent of cases respectively, metastatic malignancy from the upper abdomen, (the true Bloomer shelf) in eight and 16 per cent respectively, diverticulitis in 25 and 10 per cent of cases respectively, and endometriosis six and 12 per cent respectively. Retro-peritoneal sarcoma accounted for a small percentage. Brust listed 17% of extra-rectal masses as due to peri-rectal or pelvic abscesses at the levator level or higher. Buie did not include these in his table. Carcinoma of the sigmoid may produce an extra-rectal mass by becoming inflammatory and dropping down into the pelvis. Also, a carcinoma of the cecum can perforate and form a pelvic mass.

Green (6) gives a very interesting table, indicating by what method of examination the diagnosis was made in 284 cases of recto-sigmoid lesions:

Submitted, Oct. 4, 1948.

*From the Surgical Service, Harper Hospital.

**Present address, Marshalltown, Iowa.

Biopsy	6
X-ray	77
Gyn Study	57
Urologic study	20
Laparotomy	51
Rectal OR	55
Autopsy	18
	284

Note that a very small number needed biopsy confirmation. The X-ray was diagnostic in about one in four cases. One in five required a laparotomy. Note also the high percentage in whom the diagnosis was made by gynecological study.

THE X-RAY EXAMINATION

In most of the intrinsic lesions, one can rely upon direct visualization through the proctosigmoidoscope and biopsy for the diagnosis. In the extrinsic lesions, there is, perhaps a tendency to rely too exclusively upon the X-ray for diagnosis.

John B. Deaver (quoted by Wagner in discussion of Green's paper) (6) stated that a finger in the rectum can detect a small growth of the terminal sigmoid through the intervening rectal wall, and spoke of this area as the "blind area" by X-ray examination.

At the level of the mid-sigmoid colon and above, the X-ray examination is very accurate. At the region of the recto-sigmoid however, the large variety of irregularities in the mucosal pattern, and the confusion of extra-rectal pathology make X-ray study of recto-sigmoid lesions at times incomplete in diagnostic value. For lesions of the rectum itself, X-ray examination is of very little value. Proctologists have discussed these points in their meetings (Green, Am. J. of Surg. Symposium (6) 75:384, Feb. 1948).

Nevertheless, much can be learned by very carefully studying the X-ray films, and correlating this with what particular defect each lesion should produce. Marshak (2) brought this out with considerable exactness in his paper: Tumor masses, as fibroids and ovarian cysts, may compress the bowel without being attached to the bowel wall. They cause a gradual indentation of the barium appearance, but the mucous membrane is always intact. The area of compression may be large and the tumor mass may be visualized as a large separate shadow on the roentgen films. If they become attached as retroperitoneal sarcomas are prone to do, there is a sharp edge between the involved and uninvolved bowel, and only one side of the bowel is invaded. Benign extrinsic lesions do not ulcerate into the mucosa, but malignant ones, such as carcinoma of the ovary or metastatic carcinoma of the pelvis, may ulcerate the mucosa. In such case X-ray differentiation from an intrinsic carcinoma may be impossible.

Pelvic inflammatory disease, carcinoma of the cervix with frozen pelvis, and radiation injury from the treatment of cervical carcinoma do not cause the short constant defect with irregular marginal ragged appearance of the mucosa typical of carcinoma of the bowel. There is a more or less fixed nondistensible and non-tender constricted area of bowel.

Endometriosis may be confusing. It can cause a slight irritability of the bowel, or a long four to ten centimeter fixed constriction with smooth mucous membrane, or a complete obstruction indistinguishable from any other obstruction. Difficulty arises when a small area does not permit accurate study of the mucous membrane pattern.

Post-operative adhesions reveal either a complete or partial obstruction. The area of constriction is short and smooth with intact mucous membrane. Both sides of the bowel are usually constricted.

Sigmoiditis may produce an area of obstruction which is localized, smooth, with intact mucous membrane: all of which may disappear with subsequent examinations.

Perforation of the recto-sigmoid by foreign bodies may result in a perisigmoid reaction causing a stenotic constriction of the bowel. Usually the mucosal pattern and folds are intact with a marked amount of associated localized irritability.

Peri-rectal abscess will usually reveal a smooth compression of the rectum with intact mucous membrane. Depending on the size and position of the abscess there may or may not be displacement of the rectum from its usual midline position. If the abscess is situated high and posteriorly, widening of the retro rectal space may be demonstrated in the lateral projection. If a fistulous tract is present this may be visualized with irregularity of the mucosal pattern.

These diagnostic problems have interested several roentgenologists and surgeons. (Rankin (7), Swinton and Gillespie (1), Wilkinson (8), Swinton and Higgenbotham (9) Marshak (2), Golden (10), and Shanks (11).

We wish here to report four cases which presented diagnostic problems, and to discuss the reasons for uncertainty and confusion at the time of the initial examinations. Whatever lessons the review of each case might present, will be indicated.

Case 1. Mrs. M. S., age 57, was first seen on 7-22-47. She gave a vague history of increasing constipation for one year and a feeling of fullness and pressure in the rectum for the past three months. This had been accompanied by a constant dull ache over the lower sacrum which was accentuated by bowel movements and sitting in the straight upright position. Diarrhea was first noticed one month ago. It was persistent, muco-purulent, with never any blood or change in caliber of the stools. There had been considerable anorexia for two months and 20 pounds loss in weight.

Barium enema one week previous (7-16-47) had shown "definite roentgen evidence of an organic lesion of the rectum. The roentgen appearance is that of carcinoma." Fig. 1.

Physical examination revealed an undernourished white female who appeared chronically ill. The temperature was 98.6° F. orally. General physical examination was essentially negative. Digital rectal examination revealed a firm, somewhat bulging mass palpable in the hollow of the sacrum beneath a smooth feeling rectal mucosa.



Case I.
Fig. 1. — Peri rectal (supra levator) abscess which simulated carcinoma. Barium enema 7-16-47 (lateral view) "irregular annular filling defect in the rectum characteristic of neoplasm. Lumen four cm. when distended."

A small amount of purulent material was present on the examining finger. No blood was present. The red blood count was 4,260,000, white blood count 12,000 with an essentially normal differential count and a hemoglobin of 13.0 grams or 85%. A Frie test was negative.

The patient entered Harper Hospital on 7-25-47. Proctosigmoidoscopy under spinal anesthesia revealed considerable purulent material in the rectal ampulla. A large densely hard mass was found in the rectal ampulla along the posterior surface, covered by an intact rectal mucosa. The distal end of the mass was about three inches from the anus and it extended upward to the region of the rectosigmoid junction. At the lower portion of this mass, on the left lateral posterior wall, a sinus tract was discharging thick pus. The sinus probed lateralward for about one inch beneath the mucous membrane. There were no other changes in the mucosal pattern and no fungating masses or ulcers were seen. It was considered that the lesion was a retrorectal inflammatory mass. A biopsy taken from the sinus tract showed only "fragments of normal bowel mucosa and granulating abscess wall." Radical unroofing of the draining retrorectal abscess did not seem necessary at this time, and accordingly conservative treatment with intramuscular penicillin was administered. The mass decreased approximately fifty per cent in ten days. A barium enema on 8-5-47, was reported as follows: "a filling defect in the upper part of the rectum with associated fistula into the adjacent soft tissue. A large amount of spasm is associated with the lesion. The roentgen findings could well be explained entirely on the basis of the large perirectal abscess found upon sigmoidoscopy. However, carcinoma cannot be ruled out from a purely roentgen standpoint alone." She left the hospital on 8-6-47.

There was a gradual and progressive decrease in the size of the retro rectal mass. The patient's general condition improved. Appetite, weight gain, and normal bowel movements returned. The low sacral pain disappeared. Barium enema on 9-5-47 was as follows: "definite roentgen evidence of inflammatory lesion in the upper rectum. There appears to be some communication with the perirectal tissue, indicating a perirectal abscess (Fig. 2). Sigmoidoscopy on 9-18-47 (two months later) revealed



Case I.
Fig. 2. — 9-5-47 "Some of the Barium has trickled through what appears to be a communication with a peri-rectal abscess." (note arrow). Constricted area now is not as narrow as it was two months previously.

the mucosal pattern of the rectum and rectosigmoid to be normal. The retrorectal indurated area had almost disappeared. Communication with the patient in February 1948 revealed the patient's general condition to be satisfactory.

Discussion

Abscesses above the levator muscles are well known anatomical and clinical entities. Green's (6) recent article contains X-ray photographs of three such supralevator abscesses with cavities above the levator muscles. Anatomically, a retro-rectal space behind the rectum and a right and left peri rectal space have been recognized. Courtney (12) has recently described a fourth deep space lying posterior to the anorectum and situated between the layers of the levator muscles.

These abscesses are usually presumed to arise secondarily from infected crypts at the anal margin. The symptoms are usually those of an acute localized inflammatory reaction accompanied by a feeling of rectal fullness and sacral or coccygeal pain. The diagnosis is usually easily established by digital rectal examination, feeling a boggy tender mass outside of the rectum. Rectal malignancies, presacral cysts or tumors, and necrosis of the pelvic bones must always be excluded.

The above case represents a retrorectal abscess which spontaneously perforated into the rectum. The usual train of acute early symptoms was not evident. The original X-ray diagnosis of rectal ampullary carcinoma was disproven by adequate and thorough proctosigmoidoscopy, biopsy, repeated contrast enema examinations and close observation. Digital examination could not establish the diagnosis.

Case 2. Mrs. A. D., age 64, was seen on 12-18-47. She had been in the hospital under our care five years previously in May 1943, for an exactly similar attack. The hospital notes at that time (1943) recorded the following: "There was a history of lower abdominal crampy pain plus progressive abdominal distention of seven days dura-

tion. Obstipation has been present for four days. There is associated anorexia, nausea, and one episode of vomiting. A similar symptom complex occurring six months previously had been relieved by catharsis. Chronic constipation has been present for years. There is no history of recent change in bowel habits, no change in caliber of the stools and no blood or mucus with the bowel movements. There have been no abdominal operative procedures.

"Physical examination revealed a slightly dehydrated, but well nourished white female. The abdomen was markedly distended and tympanitic. The course of the transverse and descending colon was visible. Occasional peristalsis was noted. Rectal examination was negative. Proctosigmoidoscopy by Dr. H. B. Kallet revealed a small polypoid granuloma on the anterior rectal wall three inches above the anocutaneous junction. No abnormality was noted in the rectal ampulla or the rectosigmoid."

Laboratory findings were all within limits of normal.

A roentgen flat plate of the abdomen at that time (5-5-43) Fig. 3a. revealed enormous distention of the colon involving the transverse, descending and sigmoid portions. Gas was noted in the rectum. Barium enema revealed an inconstant area of constriction at the recto-sigmoid junction without the characteristic signs of neoplasm. The proximal colon was markedly dilated. Fig. 3b.

The marked gaseous abdominal distention responded within one to two days to enemas plus oral catharsis, and she left the hospital three days after admission. The probable diagnosis was acquired megacolon.

Mrs. A. D. was readmitted to Harper Hospital on 12-18-47. She had no difficulty during the intervening four years until five days before her present admission. Then



Case II.
Fig. 3a. — Acquired megacolon. Roentgen appearance during acute obstruction attack. 5-5-43.

severe lower abdominal cramps, obstipation, nausea, and anorexia started. Next day, abdominal distention started, and it became progressively worse. There was no passage of gas per rectum. As with her previous episode, there had been no antecedent change in the bowel habit, no change in caliber of the stools and no blood or mucous.

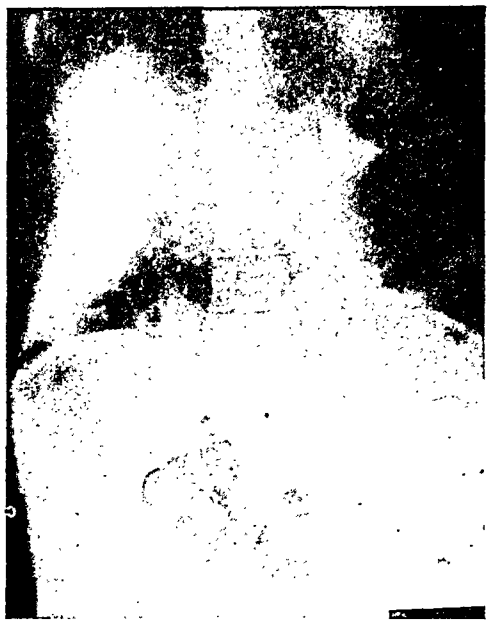
Physical examination revealed a well nourished white female, in no acute distress. The abdomen was distended, soft and tympanitic. No masses or areas of tenderness were demonstrable. The course of the transverse and descending colon was visible. Proctosigmoidoscopy revealed a narrowing and a spasm of the lower sigmoid. No intraluminal lesion was noted.

Laboratory findings were again within the normal limits.



Case II.
Fig. 3b. — 5-6-43. Barium enema. Obstruction has been relieved by enemas and oral cathartics. Note narrowing at recto-sigmoid junction.

A roentgen flat plate of the abdomen on 12-18-47 showed marked dilatation of the colon indicative of low colonic obstruction. Fig. 4a. Barium enema 12-23-47 showed



Case II.
Fig. 4a. — After four years interval of perfect health, patient had another acute attack of abdominal distention. Note similarity with Fig. 3a.

"two areas of relative narrowing of the recto-sigmoid. Their contours are smooth and there is no indication of malignancy." Fig. 4b.

Comparison with the films taken in May 1943 showed



Case II.
Fig. 4b. — Contrast enema post evacuation film 12-23-47. Area of relative narrowing the recto-sigmoid (arrow). The contour is smooth and there is no indication of malignancy.

almost identical appearances. The flat plates of the two examinations could almost be superimposed, and the barium enemas showed identical narrowed areas in the recto-sigmoid colon which had not changed.

The patient's distention responded well to enemas and catharsis. The course of the descending and sigmoid colon remained palpable on various occasions. She left the hospital in one week, entirely relieved. The probable diagnosis was again acquired megacolon. The possibility of sigmoid volvulus was considered. When last heard from, June 28, 1948, she was visiting in California, felt well, had gained four lbs. in weight and had had no further abdominal pain attacks.

MEGACOLON

Over 2/3 of the cases diagnosed as congenital idiopathic megacolon are infants, children and young people who have been constipated since birth, and who go for days or weeks without a bowel movement. This was the original group described by Hirschsprung.

A few cases have been reported in which the condition became apparent well along in adult life. Bosworth (13) believes these may have been mild cases which had been overlooked. Bockus (14) similarly states that "in my experience, constipation that has been present always, is in almost all instances iodiopathic megacolon occurring in adults."

The terms acquired or pseudo megacolon refer to a large group of cases occurring in adult life where "the same anatomical changes in the bowel wall which are seen in the congenital type are caused by a slowly developing obstruction in the region of the recto sigmoid." (Bargen 15). Some of these obstructions are: strangulation of the sigmoid, kinking, volvulus, redundancy of the sigmoid, adhesions, severe grades of chronic constipation, slowly developing intraluminal malignancy, spasm of the so-called sphincter at the recto-sigmoid, and congenital or acquired stricture of the rectum and rectosigmoid (Bacon 16). Perhaps in some of these cases, the obstruction is a secondary phenomenon and there still may be a congenital so-called "idiopathic" cause for the stricture. There is no way of proving this.

Our case might well belong to this group. We are at a loss, to otherwise explain the narrowing of the recto sigmoid, which was demonstrated in 1943 and again in 1947, and had not changed.

Regarding treatment: conservative medical management (low roughage diet, flushes, normal bowel habits, para-sympathetic nerve stimulants, spinal anesthesia, etc.) have their place: usually of moderate benefit, although a certain number of cases in each series have stayed well under medical regimes. Left lumbar sympathectomy is not entirely satisfactory. Colon resections, up until recently, carried a prohibitive mortality. For those megacolon cases complicated by a secondary obstructive factor, it is the procedure of choice (Bargen 15). Because our patient, now age 64, apparently tolerates the condition very well, nothing of a radical nature has been done.

Case 3. Mrs. J. T., age 63, was admitted to Harper Hospital on 9-4-47, referred by Dr. R. A. Sokolov. She had had a hysterectomy at the age of 46; otherwise the past history was non contributory. For the past year there was progressive constipation with some gaseous dyspepsia and slight intolerance to fatty foods. Two months ago constipation reappeared and has become progressively severe. Three days before admission there was mild abdominal colic accompanied by obstipation and abdominal distention. Vomiting occurred on two occasions within the three day period. There was no history of weakness, weight loss, bloody, or tarry stools. At no time had there been any episodes of acute abdominal pain.

Physical examination revealed a moderately obese colored female, slightly dehydrated, but she did not appear acutely ill. The temperature was 101° F. orally, pulse 100, and respiration 22. The abdomen was slightly distended. There was no abdominal tenderness, rigidity, or palpable mass. Pelvic examination revealed a normal cervical stump, with no pelvic masses. Rectal examination was negative.

The laboratory findings were within normal limits with the exception of a mild secondary anemia.

Moderate relief of the abdominal distention was obtained with enemas. Barium enema on 9-6-47 revealed "a persistent filling defect four to five inches in length, involving the sigmoid colon near the junction of the descending colon in the left iliac fossa. The persistent defect has a typical shelf like appearance and has every appearance of malignancy." Proctosigmoidoscopy on 9-9-47 was negative. There was no evidence of any intrinsic lesion of the rectum or recto-sigmoid.

Celiotomy was performed on 9-12-47. Numerous adhesions were encountered near the old laparotomy scar. The cervical stump was exposed. A bulbous, acutely inflamed appendix was found adherent to it, lying in an organizing abscess in the depth of the pouch of Douglas. This was plastered against the mesial wall of the sigmoid. Digital bimanual vaginal examination with the abdomen open demonstrated no lesion of the vaginal vault. A rectal tube was passed beyond the area of sigmoid involvement, and palpated through the wall of the sigmoid intra abdominally. There was no intrinsic sigmoid lesion. The abscess was cleaned, and the acutely inflamed appendix removed. Abdomen closed in layers without drainage.

The microscopic pathological diagnosis was subacute appendicitis with organizing peri-appendiceal abscess.

The patient's immediate post-operative course was uneventful, except for a mild phlebitis of the left leg which responded to with conservative treatment. When last seen 3-5-48, six months post-operative, her general condition was excellent. Digital rectal examination was negative. She had daily bowel movements of normal size and consistency.

DISCUSSION

The pathological pictures of appendicitis in the young and in the old are different. In the young, there is an abundance of lymphoid tissues and lymphoid vessels. Local infection predominates, and the disease is fundamentally suppurative. In an older subject there is much less lymphoid tissue. There are arterio-sclerotic changes; vessels are more tortuous, thickened and unable to dilate and relieve congestion, and circulatory impairment is much more common. It is "fundamentally a vascular disease. The initial changes are necrosis and a tendency toward massive gangrene or true tissue death." Boyce (17).

Clinically, in the young, appendicitis is usually ushered in by an acute abdominal pain quickly localizing to the right lower quadrant. Initial elevation of pulse, temperature etc., are common. The suddenness is the striking feature. On the contrary, the aged "enters the state of ill health slowly." (Lazarus 18). There is more apt to be a period of vague digestive distress, sometimes associated with diarrhea. The initial pain is frequently only a discomfort and often it does not localize at all. When it does so, the process may take days instead of hours.

In appendicitis in older individuals the abdominal walls are flaccid, there is less apt to be abdominal rigidity, and there is a uniform soft distention. The leukocyte count is notoriously unreliable, often being normal or only slightly elevated (10,000) when there is frank gangrene. Even after rupture there may be 24 hours to one week during which the patient may be only mildly uncomfortable or actually comfortable. For all of these reasons the mortality is much higher in the older age group.

If the patient surmounts an initial abscess formation, the reparative inflammatory reaction may cause varying degrees of obstruction of any part of the bowel with which it is in continuity. Bumm (19) wrote that "the history is frequently suggestive of intestinal obstruction, not the acute variety but the chronic variety due to neoplasm." Bernard and Jomain (20) recognized three groups of appendicitis in the aged; gangrenous, pseudo neoplastic and pseudo occlusive.

The case presented is one of acute appendicitis in the older age group. It conforms with the typical, more usual clinical course described above, in which the patient did not present any episode suggestive of an intra-abdominal inflammatory process. Without any localizing symptoms, an abscess formed in the pelvis contiguous with the recto-sigmoid. The secondary peri-sigmoiditis was sufficient to give clinical and roentgen evidence of carcinoma of the sigmoid colon. The true pathology was determined only by exploratory laparotomy.

Case 4. Mrs. P. K., age 81, was referred to our surgical service at Harper Hospital on 9-25-47, by Dr. W. D. Mayer and Dr. M. R. Beltman.

The patient presented a four to five year history of increasingly severe, vague intermittent generalized abdominal pain. For the past two years there has been marked flatulence and increasing constipation relieved by enemas, and increasing doses of cathartics were used. In March 1947, an attack of apparently complete obstruction had been relieved by enemas and transnasal gastric suction. There was moderate weakness and anorexia and considerable weight loss. There had been no bloody or mucoid stools. Sedatives had been required for relief or mucus stools. Sedatives had been required for relief of pain during the past six months.

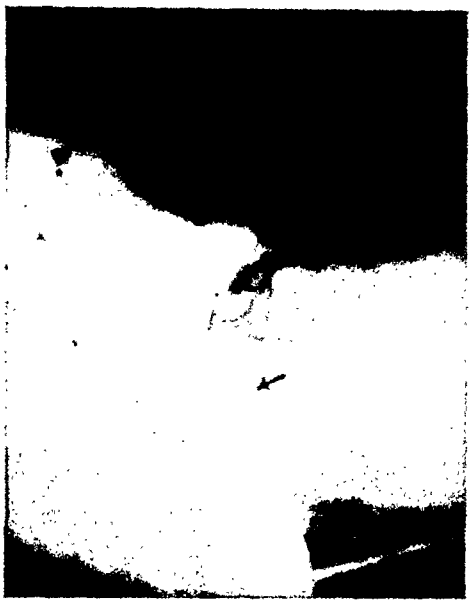
There had been numerous previous hospitalizations over the four or five year period with thorough clinical investigation. Several attempted proctosigmoidoscopies had only revealed a narrowed and tender anal orifice. Adequate visualization of the rectosigmoid had always been successful. The discharge diagnosis on each occasion had been diverticulitis of the sigmoid colon.

The roentgen findings by barium enema in October 1945, July 1947, and August 1947 had always been the same. A few diverticula were observed in the sigmoid. The remaining proximal colon was negative. A smooth annular narrowing in the rectosigmoid was present in October 1945 (Fig. 6.) and had increased in degree in July and August 1947. (Fig. 7.). The roentgen impression was that of a stricture, most likely inflammatory in nature. A malignant lesion could not be excluded.

Physical examination revealed a little old lady, quite emaciated, but alert and active for age 81. The abdomen was generally tender, slightly distended but soft. Audible peristalsis was noted. The solid organs were not



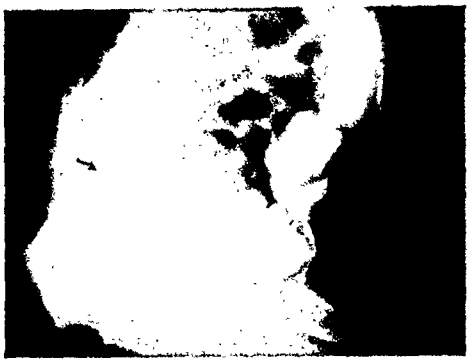
Case III.
Fig. 5. — Barium enema 9-6-47. "A persistent filling defect four or five inches in length; involving the sigmoid colon, near the junction. The persistent defect has a typical shelf like appearnce of malignancy." Laparotomy showed appendix abscess adherent to cervix stump and sigmoid, simulating carcinoma.



Case IV.
Fig. 6. — Narrowing at recto sigmoid October 1945. "The contour is smooth and not typical of carcinoma. Diag: stricture, most likely inflammatory in nature"

palpable, and no masses were detected. Rectal examination was inconclusive because of pain from an anal stricture.

Laboratory findings were as follows: Red blood count 3,660,000, Hemoglobin 10.5 grams or 68%, and a white blood count of 13,000, with an essentially normal differential. Blood chemistry determinations were within normal limits. A few days observation in the hospital revealed alternate abdominal distention with considerable discomfort, relieved completely by saline cathartic and enemas.



Case IV.
Fig. 7. — Sept. 1947 Note narrowing of stricture (2 years later). Stricture has narrowed. Laparotomy: slow growing carcinoma in elderly woman.

In view of the progressive, intermittent, partial obstruction, exploratory laparotomy was believed warranted, the probable diagnosis being carcinoma of the recto-sigmoid.

Cellotomy was performed on 9-30-47. One inch above the peritoneal fold in the pouch of Douglas, there was an annular constricting mass approximately one inch in length. The mass was typically hard, adherent, annular and felt like carcinoma. Two small calcified diverticuli were palpable above the lesion. There were no palpable mesenteric or para aortic nodes. Because of the patient's advanced age and surgical risk it was decided that abdominal perineal resection was not warranted. The growth was too low for a segmental resection and primary anastomosis. A loop sigmoid colostomy was done. No biopsy was taken.

The patient's post-operative course was uneventful. The abdominal pain, present previous to the operation was less severe. We were unable to determine to what extent the pain was associated to the chronicity of her ailments. She was discharged on 10-24-47, twenty-four days post-operatively.

Subsequent examinations revealed a continuation of the vague abdominal pain. There was progressive weight loss, weakness and anorexia. She was readmitted to Harper Hospital on 4-12-48 with bronchopneumonia and expired on 5-1-48. Autopsy was not obtained.

Discussion

Diverticuli have been reported to occur in approximately 5% of all people presenting themselves for roentgenologic examination of the colon (7). Usually it is only after the supervention of infection that the patient or the clinician become aware of their presence, since otherwise they are asymptomatic. Acute diverticulitis rarely presents diagnostic confusion, but the extensive extra luminal changes of the chronic stage (the so-called fibrous stenotic type) may be very difficult to differentiate from cancer. This was first recognized by Graser in 1898 (21). Many cases of resection of the colon for carcinoma have been reported which were subsequently proven to be diverticulitis. Although carcinoma and diverticulitis occasionally co-exist, "diverticulitis as a precursor of carcinoma is so rare as to be unique" (7).

In chronic diverticulitis the inflammatory reaction involves all layers except the mucosa. There is secondary fibrosis, constriction, spasm and narrowing of the bowel lumen, with rarely any ulceration or involvement of the mucous membrane. In carcinoma, involvement of the mucosa is the rule (22). Clinically, gaseous distention, constipation, diarrhea, rectal tenesmus and tumefaction may be present in both chronic diverticulitis and carcinoma. Blood in the stool is rare in diverticulitis, and when present one must be suspicious of carcinoma. By sigmoidoscopy, diverticulitis shows a diffuse inflammatory narrowing; while carcinoma shows chiefly ulceration involving the mucosa.

The diagnosis is usually established by roentgen examination (23, 10, 11). In diverticulitis there is spasm and irritability, a longer segment of involved bowel, the mucosal pattern is intact, and there are numerous diverticuli. In carcinoma the filling defect is constant, a short segment of bowel is involved, and the mucosal pattern is sharp and irregular. In cases of complete obstruction the differential diagnosis is almost impossible by X-ray.

The duration of the disease in either diverticulitis or carcinoma cannot be exactly determined. Our only criteria is based on the duration of symptoms before the diagnosis is made. Swinton and Higgenbotham (9), in a series of 300 cases of carcinoma of the colon, reported the duration of symptoms to vary from a few days to forty-eight months, the average

duration being nine months. Rankin (7) in a collective review of approximately 1,900 cases of carcinoma of the rectum and recto-sigmoid (his own series plus those of Neuman, Bindley and Browne) found the average duration to be 11.3 months.

That carcinoma in elderly individuals may grow slowly is very well known; also, as above described, diverticulitis may be present for years before giving rise to symptoms. A recent pathological case report from the Massachusetts General Hospital (24) was that of an 89 year old female who died of carcinoma of the recto-sigmoid. Five years previously a permanent colostomy had been done under the diagnosis of diverticulitis. The final conclusion was that adenocarcinoma had been present at the time of the initial examination, rather than that carcinoma had developed upon pre-existing diverticulitis.

Our case presented diagnostic confusion over a period of five years. Laparotomy was postponed and delayed because of X-ray findings suggestive of diverticulitis. At the time of operation a gross diagnosis of carcinoma of the rectosigmoid was made. Although microscopic section was not done, the appearance at the time of the operation and the subsequent clinical course were quite typical of carcinoma.

SUMMARY

The difficulties encountered in the differential diagnosis of recto-sigmoid lesions are discussed. Close correlation is necessary between the clinical history and examination and the various diagnostic aids. Laparotomy may be required to establish the final diagnosis.

Detailed clinical reports and discussions of four cases are presented which gave rise to diagnostic difficulties:

1. A recto-rectal abscess in an older individual which was initially diagnosed by roentgenograms as rectal carcinoma.

2. An acquired megacolon which was confused clinically with carcinoma of the recto-sigmoid.

3. A perisigmoid appendiceal abscess confused clinically and roentgenologically with carcinoma of the recto-sigmoid.

4. A carcinoma of the recto-sigmoid with symptoms of progressive obstruction over a four year period which was confused with diverticulitis.

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Volume 12
Number 5

Leiomyoma of the Rectum

By

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The term Leiomyoma is applied to tumors which are composed largely of smooth, non-striated muscle. They occur very commonly in the walls of the uterus. They are found elsewhere, as in the walls of the stomach, bladder, etc., but only rarely.

They are dense, hard masses, which on section are found to be sharply marked out from the surrounding tissues. They are further distinguished by their poverty of blood vessels. The tumor is usually composed of whorls of fibres intimately woven together.

Such tumors grow by new formation of tissues from within, expanding and compressing adjacent structures, but showing no tendency to invade nor to set up, by metastasis, similar growths in distant organs.

Microscopically, the smooth muscle fibres are arranged in paralled rows in bundles which interlace in every direction. These are embedded in an abundant stroma of connective tissue. They show no degenerative changes.

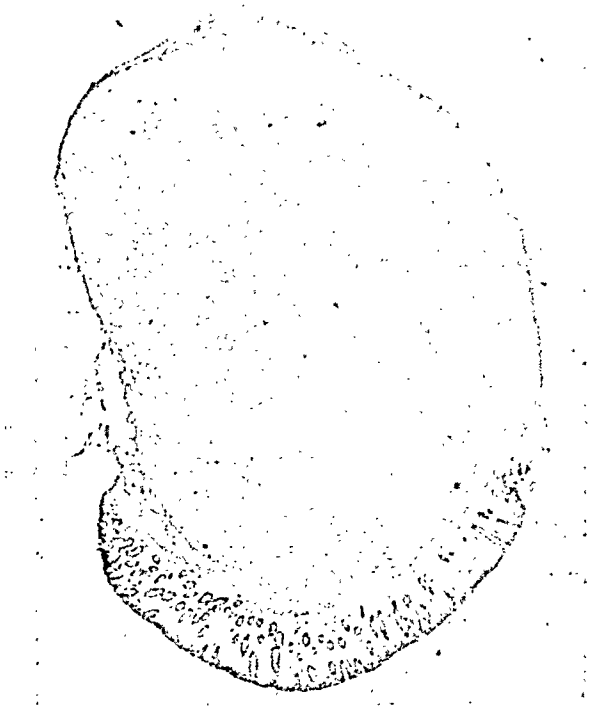


Fig. 1.

Malignant tumors composed of smooth muscle do occur. Ghon and Hintz described one which arose from the intestinal tract with secondary growths in pancreas, liver, heart, etc., and gave references to the literature which show that many cases have been observed.

It seems clear that malignant tumors spring out of benign myomata which have already existed for a long time, but the question remains as to their exact origin. They may be due to the acquisition of malignant powers of growth by the smooth muscle cells (malignant myoma), or they may be the offspring of the stroma (a true myosarcoma).

Case Report

L. P., 62 yr. old, white, male, blacksmith, entered Ward M3 at Bellevue Hospital on 5 Nov. 47.

Chief Complaint: Loose stools four times day, no bleeding, some mucus.

Present History: Referred to rectal clinic from gastro-enterology clinic with complaint of alternating diarrhea and constipation, mucus after bowel movement, and occasional mild bleeding. In the rectal clinic he was sigmoidoscoped and a polyp visualized at 17 cm. on right



Fig. 2.

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Presented at a meeting of the New York Proctological Society.

Submitted Sept. 25, 1948.

anterior rectal wall, from which a biopsy specimen was removed and sent to the laboratory. Rectal examination revealed a few moderate internal hemorrhoids (which may account for history of bleeding). Barium enema X-ray was reported as negative for any organic lesion of colon.

Biopsy reported by Dr. Von Glahn as follows: "Edematous rectal mucosa layer and underlying tumor mass, with basement membrane between being sharply demarcated and intact throughout. Tumor consists of smooth muscle fibres arranged in whorls and interlacing bundles; nuclei are large and exhibit no mitotic figures; entire mass poorly vascularized. Diagnosis. Leiomyoma."

Past History: Essentially irrelevant.

Systemic Review: Essentially negative.

Familial History: Father died at an early age from cancer. No other familial diseases.

Physical Examination: Rectal-sphincter slightly relaxed, no masses, prostate normal, rectal wall smooth and non-tender, no bleeding.

Genital-large movable cystic mass in right scrotum, not painful.

Rest-essentially negative.

Provisional Diagnosis: 1. Leiomyoma of rectum. 2. Right hydrocele.

Therapy: On 7 Nov. 47, in operating room, under morphine sulphate sedation, the base of the polyp was snared with Cameron cautery loop. Left operating room in good condition; no bleeding and no packing. Next day patient was discharged home, afebrile and no bleeding.

Operative Specimen was Reported: "No Leiomyoma seen in tissue submitted" by Dr. Von Glahn.

Follow Up: No further diarrhea; has become mildly constipated; no bleeding, and no mucus after bowel movements. On 4 March 48, another small polyp was seen on left posterior rectal wall at 13 cm. and removed completely with biopsy forceps, in rectal, clinic. No subsequent bleeding. Reported by pathologist as: "adenomatous polyp."

He will continue to report periodically for sigmoidoscopic examinations.

COMMENT

During the discussion following a paper on "Rectosigmoid" by Dr. Frederick Rankin at the 1947 AMA convention, Dr. Frank H. Lahey said, in part: "I feel that we have one chance to cure a cancer of the rectum, and that is the first one. Our clinic followed 1,800 autopsies with respect to polyps; in 4% there were polyps and of these 42% were multiple. Also, 25% of patients with cancer have associated polyps. The important thing — and this is dangerous to say — there is a type of polyp in which malignancy as reported by the pathologist is entirely within the polyp, and does not involve the base and does not spread into the mucosa. We removed 22 such cases over a series of years there have been no recurrences."

CONCLUSIONS

1. Leiomyoma does occur in the rectum.
2. A case is reported which substantiates the findings of the Lahey Clinic with respect to the fact that a tumor may be contained wholly within the body of a polyp, and not invade its base.
3. The immediate removal of any and all rectal polyps appears clearly indicated as a therapeutic and or prophylactic measure.

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Cellulose Esters in the Treatment of Constipation

By

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BULK PRODUCING SUBSTANCES have long been accepted in the treatment of functional constipation. The first of such substances used was agar, later followed by sterculia and bassora gums, and more recently, psyllium seed derivatives.

Although these have been shown to have marked advantages over harsh, habit forming chemical and vegetable drugs, the continued hunt for better bowel medication indicates dissatisfaction with them. The chief defects of current hydrophilic colloids are:

1. Lack of uniformity and miscibility.
2. Tendency to lose water in the bowel and produce inspissated stool.
3. Allergic manifestations on ingestion, i. e., abdominal discomfort and distention.
4. Gastric upset and bloating.

The vegetable gums and colloids available thus far for bowel medication vary in physiological effect. The rapid swelling of these substances in the stomach often creates a sensation of fullness that lasts for several hours and interferes with normal appetite. As the material passes through the small intestines into the colon, a great portion of the fluid is absorbed. In many cases the stool of the large bowel becomes dry and tends to produce pain as it passes through the anus. Fecal impactions have resulted from the use of available vegetable gums and colloids, requiring manual extraction following rectal surgery.

Ingestion of Karaya gums has caused intestinal cramps and diarrhea. On proctologic examinations

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Submitted Nov. 24, 1948.

acute inflammatory reactions have been observed. Patch tests on Houston valves showed local reactivity as in an allergic response.

The problem of constipation is complex because many anatomical variations enter into the picture. The fecal stream is a well recognized physiological reservoir of fluid. The hope that generally available colloids and gums will retain fluid sufficient in quantity to produce a well formed stool is not always realized. Resultant complications are painful and not without some danger.

The ideal laxative should be chemically inert, and its action should be a physical one directed toward increasing bulk in the large bowel. It should possess sufficient water retaining properties to form a normally soft stool.

The search for an improved bulk laxative led to the discovery of apparently non toxic synthetic colloids derived from cellulose esters (1). Extensive animal experimentation (2) proved that these substances were capable of producing an increased fecal stream of normal consistency without toxicity or absorption. Their application to the human problem of constipation was readily recognized and several investigations were made (3, 4).

A series of 270 patients (Table I) was used for an evaluation of the following new materials.

1. A nine per cent emulsion of sodium carboxymethylcellulose.
2. Granular methylcellulose and sodium carboxymethyl celluose.
3. Granular methylcellulose and sodium carboxymethylcellulose with anthracenes.

a. Cascara	0.1 gram
b. Comp. licorice powder	0.3 grams
c. Powd. senna	0.3 grams

4. Compressed tablets (0.75 Gm.) sodium carboxymethylcellulose.*

TABLE I

Classification of Cases Treated:

No. of Patients	Conditions Treated
120	Post anorectal surgery
75	Without digestive symptoms (controls)
50	Functional constipation
8	Atonic constipation
8	Diarrhea — food dyscrasia
5	Ulcerative colitis
4	Spastic colitis

Physiological Studies: The two cellulose esters used in this study are available in several polymerized forms which were compared to unpolymerized forms. Since the higher polymers formed too viscous a gel with resultant pasty stools, it was decided to discontinue them. Tablets and granules made up of the lower viscosity forms of methylcellulose and carboxymethylcellulose were found to be equally effective in producing normal, soft stools. The investigation was arbitrarily continued with these lower viscosity forms.

Controls. Seventy-five patients without digestive symptoms were divided into two groups:

Group A: In thirty-eight patients daily stool weights were determined for a period of one week representing the control period. It was found that in these patients the stools averaged 100 grams daily. They were then given 10 grams of sodium carboxymethylcellulose in a half glass of water followed by a full glass of water, morning and night, for one week. This dose proved to be excessive, since it nearly doubled the weight of the stools (from an average of 100 grams to 180 grams). A dosage of five grams, taken with sufficient water, increased the average weight of the stools to 140 grams, which would seem to indicate that the water retaining properties of the colloid are eight grams of water per gram of the material. The five gram dose was acceptable to this group of patients and served as a basis for the other groups studied, since it apparently proved to be an effective average dose. In terms of the new 0.75 Gm. tablets, two or three tablets three times daily would be a proper dose schedule in a majority of cases.

Group B: A group of 37 patients was given a nine per cent emulsion of sodium carboxymethylcellulose, one-half ounce, twice daily with a resultant increased stool weight of 25 grams. This form of bowel medication did not prove as satisfactory. In six patients pasty stools were formed which were difficult to pass; two patients had difficulty in passing large boluses of stool and several complained of fleeting nausea.

Post anorectal surgery: The effect of sodium carboxymethylcellulose in 120 cases of post anorectal surgery was most gratifying. There was not a single problem of obstipation or stool retention, nor was healing delayed. The stools were well formed and of such softness as to be passed with minimal discomfort.

Functional Constipation: The 50 patients in this group are of particular interest since a majority of them were "cathartic addicts," depending on some form of moderate to harsh cathartic for bowel stimulation. Sodium carboxymethylcellulose and psychotherapy were effective in correcting the bowel habits in these patients. The patients were made to understand that nature does not demand a daily bowel movement and that the use of readily available cathartics tends to produce after constipating effects which may result in serious complications.

These patients were started on four to eight grams of the colloidal laxative with about one-half the dose of their usual cathartic daily for several days, then the dose of the cathartic was gradually reduced until finally discontinued. This "weaning" process proved successful in totally replacing the cathartic with the safe, bulk producing colloid sodium carboxymethylcellulose. The patients were instructed that each dose of the cellulose ester be taken with at least a half glass of water followed by a full glass

of water in order to obtain most satisfactory results.

Atonic Constipation: Eight elderly patients with atonic constipation were given nine per cent emulsion of sodium carboxymethylcellulose with little or no effect. After a week of treatment, they were placed on five to seven grams of granular sodium carboxymethylcellulose with good response. Several, who complained of a sensation of fullness in the lower abdomen, were also given an anthracene, resulting in a favorable increase in bowel motility as well as an increase in water content of the stool. One complained of cramps, but responded well when the vegetable drug was reduced. The administration of five to seven grams of the colloid with anthracene increased the weight of the stools an average of 47 grams.

Diarrhea — Food Dyscrasia: Eight patients with diarrhea and cramps following the ingestion of offending allergens were given three grams of sodium carboxymethylcellulose every four hours with complete cessation of tenesmus and cramps within three hours.

Ulcerative Colitis: In five cases of ulcerative colitis, three grams of granular sodium carboxymethylcellulose, in a full glass of water, were given before meals. This produced fewer stools, lessening of blood and tenesmus and resulted in well formed feces. One patient could not tolerate the increased material in the lumen of the bowel.

Spastic Colitis: In X-ray proved spastic colitis, four patients responded well to the innocuous colloid. Well formed stools of good size and soft consistency were formed within one day. When medication was withheld, clinical symptoms reappeared in 24 hours but responded promptly when the colloid was again administered.

Numerous stool examinations in all types of patients showed the colloid apparently to be completely dispersed in the fecal mass. Proctoscopic examinations revealed no evidence of bowel irritation or contact allergic manifestations.

Tainter (5) showed that the action of these cellulose materials is primarily in the large bowel. They pass relatively inert through the stomach and small intestines, and manifest their action of colloidal dispersion in the right colon. There, water is retained to a much greater degree than with natural colloids previously employed.

SUMMARY AND CONCLUSIONS

Sodium carboxymethylcellulose and methyl cellulose, the former in nine per cent emulsion, as well as combinations with anthracene drugs, were studied in 270 patients for their laxative effect. Methocel proved to be a far more satisfactory colloidal laxative than any bulk material previously used for correction of constipation. The physiological action of this material produced well formed stools of unusually soft consistency as a result of the superior water retaining properties of this synthetic colloid.

The average effective dose of sodium methocel was five grams with at least one and a half glasses of water with each dose (approximately six of the 0.75 Gm. tablets) daily.

Functional constipation was succesfully treated with methocel and psychotherapy. It was found possible to wean patients away from their use of harsh cathartics and displace them with the colloidal laxative.

A nine per cent emulsion of sodium carboxymethylcellulose did not prove to be as effective as was anticipated.

The sodium carboxymethylcellulose combined with small doses of mild acting vegetable anthracenes which exert atonic effect on Auerbach's plexus, produced a desirable increase in bowel motility in eight elderly patients with atonic constipation.

Patients who have been taking the synthetic colloids for as long as 18 months have not experienced any undesirable side effects such as bowel irritation or allergic reactions.

N. B.* The materials for this investigation were supplied by the Medical Research Department of The National Drug Company, Phila. 44, Pa.

Note — Methocel Manufactured by Dow Chemical Co.

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Number 6

Complete Obstruction of the Common Bile Duct Due to Chronic Pancreatitis

A Report of an unusual case including nine operations with recovery of the patient*

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COMPLETE OBSTRUCTION OF THE COMMON DUCT caused by stones, tumors within and without the common duct, cancer of the head of the pancreas and chronic pancreatitis results in absolute jaundice. It is rather unusual for chronic pancreatitis to cause permanent jaundice. Jaundice in these cases is usually intermittent in character. In a paper read in Atlantic City last year before the Surgical Section of the American Medical Association, one of us (M. B.) reported a series of cases of chronic pancreatitis in which intermittent jaundice was a characteristic sign. The case we wish to report now is especially interesting because obstruction of the common duct was complete followed by jaundice. When jaundice is complete, one must always consider the possibility of cancer of the head of the pancreas or a tumor in the region of the papilla of Vater. The patient about to be reported was no exception. With the abdomen open, the pancreas gave the impression that we were dealing with a cancer of that organ. We contemplated performing a pancreaticoduodenectomy, but after consultation with the patient's physician (J. C. D.), we chose a short-circuiting operation.

The history is as follows:

E. C. F., age 22, female, was admitted to the Jewish Hospital 12/22/42. The chief complaint was abdominal pain. Jaundice had been present for three weeks. She stated she was perfectly well until three weeks before her admission to the hospital. Pain was referred to the back and appeared at intervals. There was some nausea before and after meals and occasional diarrhea with light colored stools was present. Itching accompanied the jaundice. Physical examination was negative except for the fact that the liver edge could be felt on deep inspiration. Laboratory studies were as follows: Hemoglobin 12.4 gm., R. B. C. 4.6, W.B. C. 8,600, Seg. 74, Ly. 26, Sugar 75, B. U. N. 11.5. The urine was acid with a trace of albumen. The Van den Bergh reaction was direct — strongly positive, indirect — 9.7 mgm. The feces contained no bile. The Wasserman reaction was negative. The patient remained in the hospital for a period of two weeks, but returned shortly after her discharge because the jaundice persisted and no improvement was noted in her general condition.

On February 10, 1943, she was seen by one of us (M. B.) in consultation. The statement at that time was made that "there was a suspicion of carcinoma of the head of the pancreas." In addition, she exhibited Courvoisier's sign with a large pyriform mass palpated in the right upper quadrant. While one could not judge by the character of the jaundice, its intensity resembled that of a malignant condition. Operation was advised.

On February 20, 1943, the first operation performed was a cholecystojejunostomy. At the same time tissue from the pancreas and a mesenteric gland were taken for biopsy. The pathological report was chronic pancreatitis. Fig. 1. The anastomosis was followed by drainage of

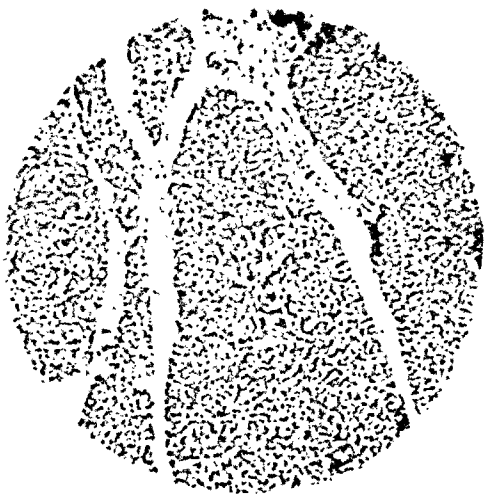


Fig. 1. — Fibrosis of the head of the pancreas causing complete obstruction of the common duct.

large amounts of bile from the wound.

On April 10, 1943, an attempt was made to close the biliary fistula. Another biopsy was obtained and the report from the laboratory was again chronic pancreatitis. There was also a subhepatic collection of bile and pus present which was drained. The pancreas seemed to have enlarged since the last operation.

For some unaccountable reason, possibly due to a hematogeneous infection, a purulent collection occurred in the pouch of Douglas. On April 26, 1943, this was drained by means of a posterior colpotomy. For the next two months the patient remained intensely jaundiced. Great difficulty was experienced in feeding the patient, and as a result, she lost much weight. Gradually, however, even though fat metabolism was greatly upset by the prolonged absence of intestinal bile, the patient improved in strength. Two and a half months after the last operation, the patient developed the signs of right lower lobe pneumonia. Shortly thereafter, she coughed up sputum which was bile tinged.

This was an unusual symptom. In a rather large operative experience on the biliary tract we had never observed a biliary pulmonary fistula. This complication must have been caused by the infection that followed the

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first operation. For months bile tinged sputum, often very copious, was expectorated.

The infection from the subhepatic space now entered the liver itself. On May 22, 1943, after resection of the 8th rib, an abscess of the liver was entered and drained.

The patient at this time was acutely ill. She continued to expectorate large quantities of bile stained sputum. Because of failing strength and nutrition, it was decided on June 26, 1943 to break down the old anastomosis of cholecystojejunostomy and perform a new one. In order to do this the jejunum had to be resected and an end to end anastomosis was performed followed by a lateral choledochogastrostomy with the aid of a T tube. A cholangiogram later showed that this anastomosis was functioning.

In August of 1943, bronchoscopic examination visualized a light yellow purulent secretion coming from the middle and lower lobe bronchi on the right side.

The T tube was not removed until September, 1943 when the old upper abdominal incision was reopened. The T tube was found kinked. The opening of the anastomosis was closed with a purse string suture. The 11th and 12th ribs were resected and the opening in the liver enlarged. All the adhesions between the liver and the diaphragm were separated. These steps were taken to eliminate the vicious circle causing the broncho-biliary fistula. The attempt was unsuccessful. A bronchogram taken in October, 1943 revealed a broncho-biliary pulmonary fistula, notwithstanding the fact that the choledochogastrostomy was patent. Fig. 2. The most distressing symptom continued to be the expectoration of great volumes of bile stained sputum.

Another attempt was made to close the fistula in October, 1943. After removal of a portion of the 10th rib, a piece of muscle was transplanted into the fistula. The wound was closed without drainage. The cough still persisted with the usual expectoration of bile tinged sputum.

The important problem seemed to be the closure of the fistulous tract. Accordingly, in January 1944, the wound in the chest was reopened and an attached piece of the diaphragm was transplanted into the fistulous tract. The wound was closed again without drainage.

Evidently our premise that closure of the fistulous tract was all important was wrong. It was apparent that bile was flowing through the place of least resistance, namely, the broncho-biliary fistula. It was also noted that the jaundice gradually disappeared when the expectoration of bile stained sputum began. Therefore, it was decided because of the absence of bile in the feces, that the choledochogastrostomy was not functioning properly.

In March 1944, the abdomen was opened again. The anastomosis was isolated and the stomach opened. No bile exuded because the anastomosis had closed. The pancreas had increased in size, completely closing the common duct. The common duct was dissected from its bed and isolated. It was bisected and the proximal end was anastomosed to the stomach over a T tube which remained in situ about a year. The former opening in the stomach was utilized. The T tube was removed on account of obstructive symptoms due to calcareous deposits of bile. Fig. 3.

The expectoration of bile stained sputum almost immediately ceased. The patient gained in weight and there was a steady improvement in health. She is well today.

SUMMARY

It is unusual for chronic pancreatitis to cause complete obstruction of the commonn bile duct. The case here reported, however, illustrates this phenomen. The symptoms were those of carcinoma of the head of the pancreas or chronic pancreatitis. Two biopsies dispelled any doubt about the cause of the jaundice. The primary operation for the relief of jaundice became infected. This was no doubt the cause of a series of eight additional operations that had to be performed. The most harassing and unusual symptom was the profuse expectoration of bile stained sputum. Following this, jaundice gradually disappeared. All efforts were concentrated then on closing the broncho-biliary fistula by means of transplantation of muscle and a portion of attached diaphragm, but they failed. Our premise was wrong. It seemed necessary to relieve the obstruction of the common duct to cure the bile tinged expectoration. The abdomen was finally opened again followed by an end to side anastomosis of the common duct to the stomach with the aid of a T tube which remained for one year. This procedure cured the patient. Stools have been normal in color since the

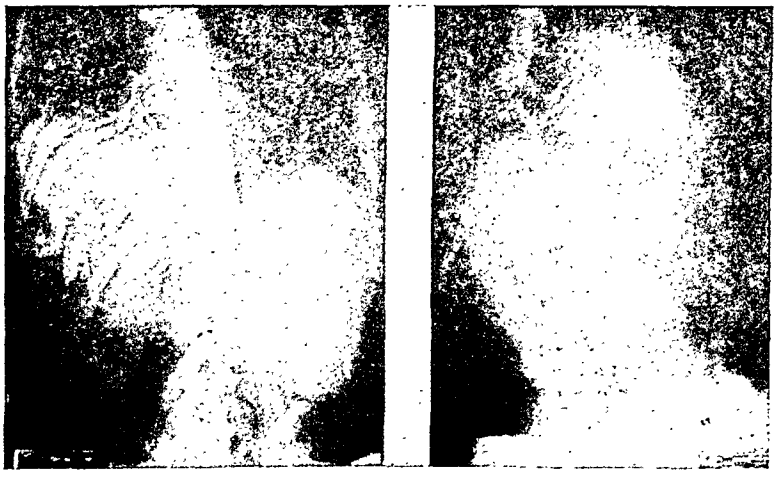


Fig. 2. — Lipiodol revealing a broncho-biliary fistula. An unusual occurrence following operations on the bile passageways.

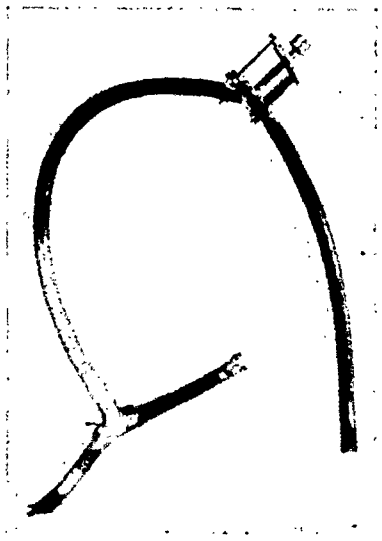


Fig. 3. — T tube remained in place one year. Note the calcareous deposits in and around tube.

last operation. Since her discharge from the hospital on April 5, 1944, she has been followed up to the present time. There has been a steady gain in weight from 98 to 150 pounds. She enjoys excellent health.

In conclusion, the patient required nine operations to restore her to health. They were as follows:

1. 2/20/1943 — Cholecystojejunostomy. Biopsy of a regional gland and from head of pancreas.
2. 4/10/1943 — Closure of biliary fistula. Biopsy.
3. 4/26/1943 — Posterior colpotomy (Vaginal Section).
4. 5/22/1943 — Rib resection. Incision and drainage of abscess of liver.
5. 6/26/1943 — Resection of jejunum. End to end anastomosis. Choledochogastrostomy (Lateral) with aid of T tube.
6. 9/ 4/1943 — Removal of T tube. Gastric closure. Thoracotomy with resection of 11th and 12th ribs.
7. 11/ 6/1943 — Thoracotomy and resection of 10th rib. Transplantation of a piece of muscle into the fistulous tract.
8. 1/15/1944 — Thoracotomy with transplantation of an attached piece of diaphragm to the fistulous tract.
9. 3/10/1944 — Choledochogastrostomy. (End to Side). Drainage: One T tube and one Penrose with gauze.

Chronic Duodenal Ulcer: Hemorrhage Due to Trauma

By

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THE ASSOCIATION OF trauma and disease of the gastrointestinal tract is infrequent but well established. Trauma is also capable of inducing complications in the presence of pre-existing gastrointestinal disease. Peptic ulcerations of the stomach and duodenum and their complications are in some instances attributable to trauma, either direct or indirect. It is the purpose of this presentation to cite a case in which trauma to the head and abdomen was responsible for hemorrhage from a chronically diseased duodenum.

CASE REPORT

History: D. O., (admission No. 172), 14 year old male, was admitted to Evangelical Deaconess Hospital on January 9, 1947 at 11:00 P. M. The chief complaints were nausea and bloody vomiting. The mother of the patient related that in the afternoon of the same day, her son played football. The participants in the game tackled each other frequently. The patient was brought to the ground quite hard on several occasions and "hurt his stomach." Later the same afternoon, about 5:00 P. M., he was sled-riding and was pushed off the sled, striking his head on the frozen ground. Within ten minutes following this episode of head trauma, he became dizzy and went home. Shortly before the evening meal, the patient felt nauseated and vomited "curdled food." The mother said he looked "green," fainted and soon vomited again. After resting in bed for a short while, the patient was somewhat relieved and attempted to partake of food. His supper consisted only of broth. Shortly after supper, he vomited again, the vomitus being dark-brown in color and containing "coffee-grounds" material and some fresh blood. The patient then became weak and clammy. The family physician arrived at about 10:00 P. M. and witnessed hematemesis containing a considerable quantity of blood. The patient was sent to the hospital immediately. On admission to the hospital, the patient still complained of dizziness and nausea. The patient did not complain of any upper abdominal pain at this time. The stool earlier in the day contained no fresh or old blood.

The parents of the patient recalled that the patient had been a "finicky" eater for the past few years. He

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would refuse certain foods, preferred sweets, milk and meat, disliked raw vegetables. He had been under-weight for several years. The stools were normal in frequency, consistency and color.

Physical examination revealed a well developed, poorly nourished, white male child appearing acutely ill, restless and pale. He weighed 78 lbs. He was cooperative and rational. The blood pressure was 98/60; pulse, 100/min.; temperature, 99.2° F.; respiratory rate, 22/min. There was some discoloration but no tenderness over the left temple. No evidence of hemorrhage was found in the eyes, ears, nose or mouth. The pupils were equal and active. At times, the patient assumed a stary expression. The neck was not rigid. Examination of the chest disclosed no lung involvement. The heart tones were rapid, of good quality and normal sinus rhythm. The abdomen was negative except for very slight tenderness in the right upper quadrant. The liver border was palpable about two fingers below the right costal margin. The spleen and kidneys were not palpable. The entrance diagnosis was hemorrhage from the stomach. Analysis of the blood on admission (January 10, 1947; 1:00 A. M.) disclosed: *hemoglobin, 13.0 grams; red blood cell count,* 3,700,000 per cu. mm.; white blood cell count, 10,000 per cu. mm.

Later in the morning of January 10, 1947 the hemoglobin reading was 10 grams (65%). The red blood cell count was 3,800,000 per cu. mm. Urinalysis revealed no albumin, sugar, acetone or diacetic acid.

Course: The blood pressure varied little in the first six to eight hours after admission to the hospital. The face and lips were pale and the pulse rate remained at 96/min. 250 cc. citrated blood was administered in the morning following admission. Ascorbic acid was also added. On January 11, 1947, the patient was much improved; vomiting ceased. A tarry stool was passed on January 11. The hemoglobin fell to 9.5 grams and the red blood cell count to 3,100,000. On January 12 the blood pressure fell to 70/48 and the patient passed another tarry stool. 250 cc. and 500 cc. citrate transfusions were administered January 12 and 13, respectively. Strained gruel and milk feedings were started on January 10. The red blood cell count and hemoglobin on January 14 were 1,500,000 and 49%, respectively. After January 15 the blood picture improved; on January 20 the red blood cell count was 3,500,000 and hemoglobin 11 grams.

Roentgen examination of the upper gastrointestinal tract was performed on January 17, 1947, eight days following admission. The opacified esophagus showed no intrinsic or extrinsic abnormality. There was no distortion of the gastric air bubble. The stomach was slightly dilated and exhibited exaggerated peristalsis and slight pylorospasm. After a short delay the duodenal bulb was opacified. Serial studies showed a marked deformity of the bulb. The mucosal pattern was distorted, the altered markings radiating toward a static area of opacity measuring almost one cm. in diameter (Fig. 1). Some tenderness was also present. The duodenal sweep was not widened. The stomach was empty of all opaque material four hours later.

Impression: 1. Deformity of duodenal bulb due to chronic inflammatory changes and cicatrization; 2. Acute duodenal ulcer. The extensive fibrotic changes in the duodenum were obviously due to chronic inflammatory disease and the ulcer crater, source of bleeding, was evidently the result of recent trauma.

Subsequent Course: The patient thereafter made an uneventful recovery and was discharged from the hospital on January 20, 1947, 11 days following admission. On March 8, 1947 follow-up roentgen studies were performed. At this sitting the stomach was of normal tone, contour, distensibility and peristalsis. Although the deformity of the duodenal bulb was still present, the large crater previously observed was no longer visible (Fig. 2). No tenderness could be elicited and gastric motility was still normal. So far as we know, the patient has continued in good health.

COMMENT

Before any lesion in the gastrointestinal tract can

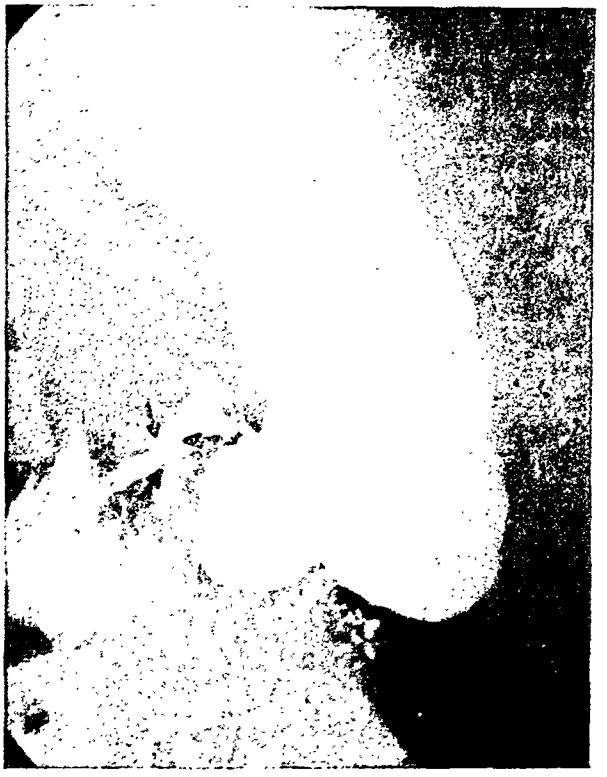


Fig. 1. — Roentgenogram of opacified stomach and duodenum January 18, 1947. Stomach is slightly dilated. A large ulcer crater (arrows) is seen in the midst of the markedly deformed duodenal bulb.



Fig. 2. — Follow-up examination on March 8, 1947 discloses healing of the acute ulcer and persistent deformity of the bulb.

be attributed directly to trauma the postulates of Liniger and Molineus (1) must be fulfilled. They

are (Crohn (2)) as follows: (1) No known similar disease must have existed prior to the trauma; (2) The trauma must have been sufficient to act as a possible causative factor; (3) The trauma must have been immediately followed by active symptoms (usually 24 to 48 hours); (4) The disease appearing after the trauma must have presented clinical symptoms recognized as associated with the particular morbid state.

The case presented above represents an example of exaggeration of symptoms following trauma in a previously diseased duodenum. On the basis of the clinical history and roentgen appearance there can be little question concerning the association of trauma and hemorrhage in our patient. Development of the acute ulcer is attributed to abdominal and/or intracranial trauma. The most interesting aspect of our patient is the possible or probable influence of head trauma in the causation of an acute ulcer and hemorrhage. A few episodes of abdominal traumata and at least one of head injury preceded hemorrhage by a few hours. Hemorrhage and/or perforation may result directly from trauma in patients with or without peptic ulceration of the stomach or duodenum. Such trauma need not be applied direct to the abdomen. External violence to the head might result in "contrecoup" effects on the gastrointestinal tract.

Cushing (4) alludes to the apparent relationship between the nerve centers near the base of the brain and visceral function. Patients who prior to pituitary gland and cerebellar surgery had not had gastric difficulty might have a severe gastric hemorrhage or actual perforation of the stomach a day or two after the surgical procedure. Cushing reports similar complications following localized infection of the base of the brain. According to Cushing (5) injury to the diencephalon causes irritation of the fiber tracts and vagal centers within the brain stem which in turn produces vagal, sympathetic and parasympathetic stimuli responsible for motor, secretory and circulatory changes in the upper gastrointestinal tract. The latter changes are supposedly most important. It is believed that ischemia if sufficiently prolonged subsequently leads to necrosis and ulceration. Acute ulcers may be seen within a few hours after head injury. There is reason to believe that the head injury in our case was sufficiently severe to cause hemorrhage from a previously diseased duodenal bulb.

SUMMARY

Hemorrhage from the gastrointestinal tract following trauma is reported in a 14 year old male with a chronically diseased duodenum. It is proposed that abdominal and head trauma were directly and indirectly responsible for the development of an acute ulcer and hemorrhage. Brief comment is made concerning the relationship between the vital centers and gastrointestinal function and disease.

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NUTRITION

Dry Feedings in Gastric Motor Delay

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and

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IN 1908 one of us (1) reported favorable results in the treatment of gastric motor delay with the use of high fat, high protein diets. An incidental detail in this procedure was the use of fluids by rectum only, the food being entirely dry and finely divided. Water by mouth was held to an absolute minimum. During the past 40 years this same writer has had occasional opportunities to employ a "dry diet" mainly in cases of obstructive peptic ulcers, with a few very gratifying results where all other methods of medical management failed. Recently an attempt was made to evaluate this type of treatment particularly in view of the statements by Wolf and Wolff (2). These authors mention differences in

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gastric motor function of their subject in reaction to fluids as compared with dry foods. They noted temporary inhibitions of peristalsis following introduction of various fluids, while no inhibition occurred after dry food.

Another factor was considered, namely the psychic one. After long periods of liquid diet some patients, particularly those who dislike milk, appreciate a change to dry food. The change in consistency of the diet, alone, seemed to gratify some patients who had adopted a pessimistic attitude toward the more liquid diets. Furthermore smaller volume of feedings might permit a dilated stomach to regain its tonus, and more calories per volume could be given.

Accordingly, patients with benign gastric or duodenal ulcers and motor delay were tried on "dry" diets after they had failed to improve on conventional "Sippy" or "Meulengracht" diets. The usual antispasmodics and antacids were continued, as well as sedation. The diet consisted mainly of finely divided hard boiled eggs, dry cottage cheese, cooked cereal without added cream, crackers, minced chicken, mashed potatoes, and rice. Butter was added to the cereal foods. Initially at the end of each day any food remaining in the stomach was removed by aspiration with an Ewald tube.

Reports of representative cases:

Case 1. Dr. W. T., a 67 year old man admitted June 3, 1948. Patient had "hunger pains" for five years, had been vomiting constantly for previous six weeks. He had lost 80 lbs. despite treatment with milk and cream, antacids, etc. X-rays showed over 50% retention in five hours and evidence suggestive of a duodenal ulcer. Physical examination showed evidence of marked weight loss. His heart exhibited frequent extrasystoles. The liver was palpable on deep inspiration. Blood and urine examinations were essentially negative. The sedimentation rate was moderately elevated.

The patient was placed on a stationary "5th day Sippy Diet," with antispasmodics, antacids, and sedation. Nevertheless he continued vomiting with severe "bloating" and nocturnal gastric residuals of about 450 cc. He was started on "dry feedings" as described above, and immediately experienced relief of his "bloating" and vomiting. His nocturnal residuals diminished, and after five days he started gaining weight. Intravenous glucose 5% in distilled water, 1,500 cc. daily was tolerated without complaint because of the improvement in general well-being. X-rays showed about 25% retention in five hours and he was then allowed fluids by mouth. Follow-up report several months later was very satisfactory.

Case 2. J. R., 52 year old man, admitted on August 15, 1947. This patient was found to have a duodenal ulcer in 1936 by X-rays. In the interim he had eight hospital admissions for bleeding and/or vomiting.

Two weeks before admission he again had pain, vomiting, once of coffee-ground material. Physical examination showed evidence of marked dehydration. Gastric aspiration revealed 800 cc. residual. He was placed on a "First Day Sippy Diet." He continued vomiting and maintained high gastric residuals up to 1,500 cc. After five days he was placed on "dry feedings" with intravenous fluids. His evening residuals dropped to 400 cc. the next day and to 75 cc. by the fifth day of this regimen. He was then placed on a convalescent ulcer diet which he tolerated well. Surgery was advised and performed on a subsequent admission.

Case 3. E. K., a 53 year old female, admitted on May 11, 1948.

This patient had had ulcer symptoms for two years, generally relieved by food and alkalies. However, for one month prior to entry she had repeated bouts of vomiting, also severe pain. Physical examination showed moderate obesity, tenderness in epigastrium, and moderate hypertension. Blood, urine, and stool examinations were normal. An electrocardiogram was normal. X-rays disclosed evidence of a duodenal ulcer with 50% retention in four hours.

On entry she had over 900 cc. gastric retention and this was maintained whenever her diet was raised beyond that of a milk and cream regimen. After about three weeks she was started on "dry feedings" and parenteral fluids. She complained bitterly of the thirst and did not like her new diet. Nevertheless she had no pain or vomiting and in four days she was permitted 200 cc. fluids by mouth. Oral fluids were gradually increased but she was cautioned not to exceed five glasses daily. She returned to the hospital later for surgery which was performed without incident.

These last two patients were tided over their acute episodes and delivered to surgery in much better condition than they had been for many weeks. No fortified foods or expensive parenteral fluids were required. The diet was selected to some extent by the patient, did not place any extra burden on the diet kitchen or nursing staff, and even when disliked by the patient seemed rather successful. It is entirely possible that the improvement was merely coincidental and not the result of restricted oral fluids. However the improvement was so immediate that it did not seem merely fortuitous.

Occasionally a somewhat different type of case can be handled satisfactorily in this manner, as the following history illustrates:

Case 4. L. McK. a 65 year old man entered the hospital on August 5, 1947.

Patient had had a resection of carcinoma of ascending colon three years previously. He felt well until six months prior to entry when he began losing weight and developed symptoms of partial intestinal obstruction relieved by self-induced vomiting. A mass could be felt in the right upper quadrant of the abdomen and peristaltic waves were visible passing from left to right in this region. Laboratory data were essentially negative except for rather severe anemia. X-rays revealed a tremendously dilated stomach, evidence of obstruction in the second portion of the duodenum, and about 90% retention in four hours.

The patient was given a selective general diet, soft diet, and then a liquid diet, but gastric lavages contained persistent residuals of over 1,000 cc. He was finally placed on "dry feedings," all fluids administered parenterally.

His residuals dropped to generally less than 250 cc. vomiting ceased, and he was then gradually allowed a more liberal diet and small quantities of fluids by mouth. After about a month he was operated on, a malignant growth surrounding the duodenum was noted, and a gastro-enterostomy was performed.

The concentrated food in this case merely helped relieve the distension by presenting a smaller volume of material for the stomach to handle. With relief of distension and improvement in tonus, the stomach was able to propel the material through a narrowed duodenum, since it was unlikely that the lumen increased in size during this time.

SUMMARY

The use of a "dry" diet with all fluids administered parenterally for treatment of refractory gastric motor delay is described. The mechanical factor is considered of some importance, particularly in view of reported inhibition of peristalsis by fluids and not by solids. The psychological value of a change to solid food is mentioned. Also important is the added caloric value, volume for volume, which these foods possess over liquids. The smaller volume of feedings may help a dilated stomach regain its tonus.

Pyloric obstruction, whether spastic or organic, is rarely complete; even if there is gross retention, entire withdrawal of all oral feeding as usually practiced may not be necessary or advantageous. A satisfactory though limited gastric function in terms of nutrition can often be attained by the technique described.

This procedure is not advocated as one of choice in the treatment of peptic ulcer or any other lesion. Its value lies in the fact that it will frequently, as a temporary measure, tide the patient over the emergency of a gross gastric retention until the indicated medical therapy can be instituted or surgical measures taken if necessary. If so used, the results may be gratifying.

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Nutrition Notes

Relapse in Pernicious Anemia

It is always difficult, in pernicious anemia, to detect the beginning of a hematological relapse, because the drop in cell count and hemoglobin values is usually not a fast one, and because we are always uncertain what the individual's normal cell count used to be, prior to the onset of the disease. It is undoubtedly false to assume that if adequate liver therapy cannot elevate the red blood cell count above 4,000,000 per cc., that this represents the normal red cell level for this individual. Some cases respond well to liver extract and some do not. We do not agree with certain current doctrines that advise the use of liver extract alone in the treatment of all cases of Addisonian pernicious anemia, because the metabolism of erythropoiesis and of hemoglobin synthesis may be greatly complicated by two factors. First, the patient may have a quite independent defect in iron metabolism, in other words, a secondary anemia, as a complication. Second, there may be great difficulty in forming the proximate metabolites required for the production of red cell stroma material. The defect in iron metabolism may be overcome by the administration of iron in some form agreeable to the patient, and the iron and ammonium citrate is generally better tolerated by these patients than iron gluconate. The deficiency in stroma material not infrequently may be made good by administering such organic material as the extract of spleen and bone marrow. By such a combination of iron with spleen and marrow, in addition to the liver extract, we not infrequently obtain a palpable rise both in hemoglobin and red blood cell count, in cases where a subnormal plateau has been maintained for many months. Since this maneuver has been of distinct advantage to the author, he has no hesitancy in recommending for this purpose a preparation which combines all these additional elements in a most palatable manner.*

Furthermore, we do not agree with certain current doctrines which suggest that liver extract be given only parenterally. While such a method of administration works satisfactorily for maintenance purposes in the majority of cases, there are other cases in which it does not work at all well. The reason is not clear, but presumably it is related to an inability of the patient to store the active principle (vitamin B_{12}) in the liver. Once an intramuscular injection is made containing, say 15 units, the patient is presumably able to "consume" only one or two units in the ensuing 24 hours for purposes of hemopoiesis, and if the balance cannot adequately be stored, it is completely lost through excretion. The use of *oral* liver extract concurrently and between parenteral injections ensures a constant absorption of vitamin B_{12} in quantities sufficient to meet the needs of the uncomplicated case. Yet, faulty absorption must in some cases be considered a complication.

It is not too certain where vitamin B_{12} is stored, or how it is stored, but there are some indications that it is stored in the liver and may actually accompany the bile circulation. The author has had two cases in which severe neurological and hematological relapse suddenly occurred following modified Meltzer-Lyon drainage of the gall bladder, using magnesium sulfate in concentrated solution. Perhaps magnesium sulfate ought not to be used as a laxative in cases of pernicious anemia which give any evidence of difficulty in management. We know that several years ago it was discovered that ox bile on intravenous injection into patients in relapse produced a good reticulocyte response, which supports the idea that vitamin B_{12} is at least excreted via the bile.

In any case, where the response to liver extract is not satisfactory, and where infection and endocrinous

*Maltine with Spleen-Marrow, Iron and Vitamins A and D. The Maltine Company, New York.

dyscrasias can be ruled out, the possibility of a defective and independent disorder of iron metabolism should be kept in mind and iron administered. It should also not be forgotten that spleen and bone marrow at least appear, in some difficult cases, to supply missing metabolites, and that wherever faulty storage of the active principle is at fault, oral administration is a necessity.

Canada and the Eskimos

The Eskimo race has been weakened by malnutrition as well as by diseases introduced by the white man. The federal government of Canada, recognizing the need for direct assistance, has made, and is now making, strong efforts to improve the diet of the Eskimo and to raise his living standard. In line with this effort, Canada has extended to the 8,000 nomadic Eskimos along the bleak northern shores of her mainland and throughout the islands that dot the Arctic Ocean, the benefit of family allowances which the entire Canadian population enjoy in virtue of their having children. All such allowance payments must be made in kind from a prepared list distributed to every Northland trader. Posters in English as well as in Eskimo syllabics inform the Eskimos what they may purchase in their allowance credits, it being understood that these gratuities are solely for the benefit of their children. Among the food substances made available are dried or evaporated milk, pablum, vitamin B flour, oatmeal, sugar, corn syrup, molasses, marmalade, jam, fresh or powered eggs, peanut butter, cheese, canned or fresh meat, fresh or dried fruit, canned tomatoes, green or dehydrated vegetables, rice, beans, salt, baking powder and lard.

Inasmuch as the indigenous diet of the Eskimo consists largely of fish, game and blubber, it will prove of interest to the nutritional scientists to observe, in the course or time, what beneficial effects these supplementary food articles exert on the general health and disease incidence among this brave and austere race of men.

Study of Canned Foods

A six-year, nation-wide program of scientific research into the nutrient values of canned foods was recently described as "providing more knowledge about canned nutritive values than had become known since the discovery of vitamins at the turn of the century."

The research, initiated before Pearl Harbor and carried on in the laboratories of nine leading universities by such top-ranking scientists as Dr. C. A. Elvehjem, discover of niacin, was so summarized by Dr. E. J. Cameron of Washington, D. C., research director of the National Canners Association, in a report to the board of directors of the Association at the Palmer House.

The laboratory findings revealed for the first time on a national scale the content of canned foods in terms of calories, proteins, carbohydrates, fats, vitamins A and C, four of the B vitamins (thiamin, niacin, riboflavin, and pantothenic acid) as well as such minerals as iron, phosphorus and calcium.

In discussing the importance of the research and its findings, Dr. Cameron said, "The new knowledge unearthed by the research program enables homemakers, military officials and institutional dietitians for the first time in history to use canned foods on a day-to-day basis with complete data on the vitamins, minerals and calories to be found in more than forty different canned foods that are consumed in largest quantities."

At a luncheon held in conjunction with the meeting of the industry association, Dr. Elvehjem, who is dean of the Graduate School at the University of Wisconsin, commented on the significance of the research program and the progress in nutritional knowledge which has been made.

"I believe it is accurate to say," he asserted, "that the canned food nutritional research which has been sponsored by the canners and can manufacturers of the United States is one of the most comprehensive and valuable programs of scientific investigation that has ever been undertaken in the processed food field. The findings which have been developed represent a very real contribution to the public welfare as well as to the technological advancement of the canning industry."

Highlights of the new nutritional knowledge clarified by the research program were outlined today as follows:

1. High ratios of vitamins, minerals and calories are retained in canned foods packed for standard commercial use.

2. Normal dietary requirements for nutritional factors supplied by cooked foods of various types may be met through selective use of canned foods with special characteristics in terms of caloric, vitamin and mineral content.

3. On-the-spot scientific processing of fresh products, as practiced in the commercial canneries, plus application of standardized quality control methods, retains relatively large amounts of essential nutrients in contrast with many types of home cooking which disperse nutritive elements or destroy essential elements by over-heating. The research illustrates the fact that a can actually functions as a miniature pressure cooker.

4. Protection of heat-sensitive nutritive elements, notably thiamin and vitamin C, may be fostered indefinitely in canned foods by avoidance of high-temperature storage conditions.

5. New nutrient tables, showing precise national averages for 42 staple products most widely in demand, provide the soundest basis for controlled medical and institutional use of canned foods that has thus far been developed.

6. Notable improvements in food-research methods have been effected, through development of standardized techniques to compensate for seasonal and geographic variables and eliminate non-uniformity of research methods (a weakness that has limited the reliability on past research data on both canned

foods and raw foods).

7. Home economists, upon whom millions of American women rely for diet guidance, now have available scientifically proven food composition tables for use in selecting canned foods with differing characteristics, in terms of caloric content as well as vitamin and mineral characteristics.

8. Detailed information is now available to guide homemakers on the most efficient and economical use of canned foods, through avoidance of home preparation methods which waste essential nutrients. Example: A large percentage of the nutrient value of canned foods has been proved to be contained in the liquid portion, hence the need for housewives to reduce the liquid volume and serve the concentrated liquid along with the solid portion.

Abstracts on Nutrition

SUNDARESON, A. E.: *A comparative histopathological study of infantile cirrhosis of the liver of India with cirrhosis of the liver in infants of Edinburgh.* (J. Indian Med. Assn., October 1948, Vol. XVIII, No. 1, 107).

In a comparative study of six cases of "Infantile cirrhosis of the liver," of India and 10 cases of "Cirrhosis of the liver in infants" of Edinburgh, it was found that the disease as occurring in India closely resembled five of the Edinburgh cases. It is obvious to the author that cirrhosis of the liver in infants everywhere, including America, is not rare, even when syphilis is ruled out, as it was in his cases. In Calcutta, India, alone, 700 deaths per year occur from infantile biliary cirrhosis. The six Indian cases subjected to histopathologic examination conformed to five of the cases in Scotland and constituted together the main type of lesion, characterized by inflammatory infiltration of the larger hepatic veins with thickening of the veins themselves, interstitial fibrosis, proliferation of biliary canaliculi, bile stasis and parenchymatous necrosis and regeneration. Five of these 11 cases showed a definite familial incidence. The author believes that the infantile liver may be damaged by maternal toxins obtained transplacentally or through mother's milk and he is furthermore of the opinion that the absorption from the intestine of some proteins of large molecular size may severely injure the liver whose cells are particularly adapted to the absorption of such molecules in view of the sluggish hepatic circulation; but he brings into his argument the probability that such proteins are toxic only in the absence of nucleic acid and a high concentration of protein in the diet. Since this protective action of the diet is lacking so frequently in India because of poverty, as well as the popularity of meatless dietary regimes dictated by religious principles, he is inclined to attribute the high incidence of infantile hepatic cirrhosis in India to this dietary factor. Unfortunately the article does not present the clinical findings of any of the cases.

BERRY, R. E. L., LOB, V. AND CAMBELL, K. N.: *Potassium metabolism in the immediate postoperative period.* (Alex. Blain Hosp. Bull., Feb. 1949, Vol. 8, No. 1, 34-41).

During the immediate postoperative period, potassium is excreted in the urine in excess of that anticipated from the breakdown of protoplasm. The necessity for the adjustment of the various compartments of body water to the administration of intravenous fluids is considered the most important factor involved. This adjustment is accomplished at the expense of the intracellular fluid, although other contributing factors may be: (1) anesthesia and trauma of operation, (2) load of sodium chloride, (3) dehydration, (4) hemorrhage at the time of operation and (5) glycogenolysis. Losses of potassium observed in these patients is large, but constitute only a small fraction of total cellular potassium, and signs of intracellular postassium deficit were not observed. There appears to be little necessity to reinforce solutions given parenterally with potassium in short term therapy, provided that pre-operative preparation has been adequate.

POPPER, H. L.: *(Michael Reese Hosp., Chicago): Acute pancreatitis. An evaluation of the classification, symptomatology, diagnosis, and therapy.* (Am. J. Digest. Dis., 15:1-4, January, 1948).

The proper conservative therapy has as its aim the diminution of the secretory activity of the pancreas and relief of spasm of the sphincter of Oddi. Anything that stimulates the vagus nerve will stimulate the pancreas; therefore, prostigmine, as well as morphine or its derivatives, should be excluded. Hyperglycemia has a pronounced stimulating effect by way of the cholinergic mechanisms, and hypoglycemia also has a marked vagotonic action. Parenteral glucose administration, as well as the regulation of the blood sugar by Insulin, must therefore be handled with extreme care. *(Courtesy: Diabetes Abstracts)*

SEED, LINDON: *(Univ. of Illinois, Chicago): Periodic paralysis in a patient with exophthalmic goiter controlled by 6-propylthiouracil.* (West. J. Surg., 55:640-46, December, 1947).

The disease is characterized by repeated attacks of flaccid paralysis commonly appearing after prolonged periods of rest. It was shown that in most patients there was a significant drop in serum potassium, and that in most instances the attacks could be terminated by the administration of potassium salts either intravenously or by mouth.

In this case symptoms were not relieved by potas-

sium medication. The patient described had the unmistakable symptoms of periodic paralysis, which disappeared with 6-propylthiouracil medication but promptly recurred when the drug was discontinued. *(Courtesy of Diabetes Abstracts)*

MACLEAN, ANGUS L. AND BRAMBEL, CHARLES E.: *(Johns Hopkins): Dicumarol and rutin in retinal vascular disorders.* (Am. J. Ophth., 30:1093-1108, September, 1947).

Four cases of diabetic retinopathy showed improvement of visual acuity and absorption of hemorrhages when treated with dicumarol. No increase in capillary fragility was observed in this group of patients. However, two of four patients were treated with rutin simultaneously with dicumarol.

The only logical explanation for ophthalmoscopic improvement probably lies in the fact that thrombotic tendencies were inhibited by the anticoagulant, with resulting increased vascular efficiency followed by clearing of the involved retina. Final critical evaluation must await findings from larger numbers. Dicumarol and rutin possess therapeutic value in venous thrombosis and in the absorption of retinal hemorrhages. The rate of absorption of blood extravasations was greater and more rapid than it would have been had no treatment been given. This was especially true in the diabetic cases. *(Courtesy: Diabetes Abstracts)*

KOMETIANA, P. A., GOGOLASHVILI, SH., AND DOLIDZE, S.: *(Georgia USSR): The relation between the resynthesis of glycogen and the distribution of potassium in muscular tissue.* (Soobshtchenija Akademii Nauk Gr. SSR, 5:269-78, 1944 (Abstr. from Excerpta Medica (Endocrinology), 1:149, October, 1947).

A determination was made of the potassium distribution in muscular tissue in the process of resynthesis of glycogen. The experiments were carried out on frog hind limbs, prepared according to the method of Laeven-Trendelenburg and perfused with Ringer's solution in which potassium chloride was replaced by an equivalent amount of lactate. Simultaneously, fatigue was instigated directly by electric stimulation. When complete fatigue was obtained, Ringer's solution with nitrogen was passed through one limb and Ringer's solution enriched with oxygen through the other. In this way, aerobic and anaerobic rest of the muscle was achieved. The results showed that in the process of aerobic rest of fatigued muscle, together with the resynthesis of glycogen, the intracellular phase of muscular tissue becomes enriched with potassium. *(Courtesy: Diabetes Abstracts)*

LEGER, LEE H.: *(Kansas City, Kans.): Hypoglycemic states.* (Am. J. M. Technol., 13:295-303, November, 1947).

In this review of two hundred and twelve (212) cases with abnormal glucose tolerance curves, a wide variety of functional and pathological conditions were encountered. However, it is representative of the group one would expect to find when considering the condition that would cause alterations in carbohydrate metabolism of a hypoglycemic nature.

Portis and other investigators have pointed out that neurasthenic fatigued patients show flat glucose tolerance curves which subsequently return to normal by the use of a diet low in carbohydrate and high in proteins. The neurasthenic or psychoneurotic seldom has severe hypoglycemic symptoms.

The effectiveness of the high-protein, low-carbohydrate diet is due to the slow rate at which dextrose is derived from proteins, resulting, therefore, in no elevation in blood sugar and consequently in no secondary fall. The diet should contain about two Gm. of protein per kilogram of body weight, with from 50 to 75 Gm. of complex carbohydrate. Fats sufficient to maintain calories are given. No free sugar should be contained in the diet.

Hypoglycemia usually produces the most disturbing symptoms in these cases. Fortunately these symptoms can be promptly relieved by the diet previously described provided the specified amount of protein is ingested. The author has found belladonna and phenobarbital the sedatives of choice. *(Courtesy: Diabetes Abstracts)*

LACKEY, ROBERT W.: *(Southwestern Med. Coll., Dallas):* Effect of the injection of glucose into the cerebrospinal fluid. (Science, 106:618, December 19, 1947).

Recently, Marinelli and Giunti have reported that injections of relatively small amounts of glucose into the cerebrospinal fluid by way of the cisterna magna result both in the dog and in man in a rapid and pronounced fall in glucose content of the blood, followed by a slower return to basal values. Marinelli and Giunti infer that the glucose content of the cerebrospinal fluid represents a direct chemical stimulation upon the glycoregulatory nervous centers, resulting in functional changes affecting the glucose level of the blood.

In an attempt to corroborate the findings, six normal, docile dogs were selected; and after a fast of eighteen hours, blood samples were taken. Without the use of an anesthetic, a needle was placed in the cisterna magna; two ml. of cerebrospinal fluid were withdrawn; and two ml. of a five per cent solution of glucose were injected. Blood samples for glucose determinations were taken at 5, 15, 30, 60, and 120 minutes. Lowering of the glucose level of the blood was in no instance obtained following intracisternal injection of glucose solution. There appears to be a definite tendency toward an increase in glucose content of the blood during the second hour of the tests. *(Courtesy: Diabetes Abstracts)*

HOUSSAY, B. A., AND CARDEZA, A. F.: *(Instit. of Biol. and Exper. Med., Buenos Aires): Treatment of meta-alloxanic diabetes by Insulin, phlorhizin, or suprarenalectomy in the dog.* (Rev. Soc. argent. de biol.,

in size following the prolonged administration of massive doses of vitamin B complex, but this is less spectacular than the case of Davis and Culpepper.

Their conclusion that hepatic cirrhosis itself may be the etiological factor in some cases of cardiac decompensation is sufficiently revolutionary as to provide possibly a new and heretofore unsuspected element in the study and treatment of heart disease. Certainly, in cases of cardiac disease in which enlargement associated with insufficiency, appears to rest upon no discoverable cause, one ought to bear in mind the possibility of cirrhosis of the liver, even though, at the moment, no tangible evidence of liver disease can be detected.

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NOTE ON SOME EXPERIENCES WITH GASTROINTESTINAL ALLERGY

A RECENT NEWSPAPER ITEM reported the story of a man who "cured" himself of gastrointestinal difficulties by a 41-day starvation regime with coincident loss of 81 pounds. The thought occurred that his symptomatic relief may have been due to removal of allergic foods from his dietary intake, and stimulated me to write this brief report of my experiences with gastrointestinal allergy.

Eighteen years ago a young man came to see me with a history of abdominal pain of many years' duration. He had consulted innumerable physicians and had six X-ray examinations of the gastrointestinal tract, all of which were purpotedly negative.

Dr. Beck of Vienna had just introduced me to intragastric photography at that time. I obtained some photographs of this patient's stomach which showed small lesions of the mucosa resembling canker sores. The patient was placed on a special diet with medication consisting of ant-acids, anti-spasmodics, and sedatives, with resultant rapid relief. However, the relief lasted only until Zwieback was added to his diet. He thought that perhaps Zwieback was too coarse, but even when soaked in milk, it caused some pain. I suspected that the "canker sores" that appeared in the pictures of the gastric mucosa might be of allergic origin and therefore eliminated wheat from the diet. I did not see this patient again for many years until he came in with a common cold just two years ago, reporting that he had had no gastrointestinal difficulties since, and had been able to add wheat to his diet again.

In 1935, a young lad came into my office with a large erosive ulceration at the corner of the mouth. Scratch tests with food extracts were made. There was a violently positive reaction to cow's milk and goat's milk. The elimination of milk from his diet resulted in rapid improvement and this strengthened my impression that the mechanism of the mucosal ulcerations seen in the stomach of the previous patient was allergic.

Since that time, no patient with gastrointestinal complaints has been treated in my office without consideration of the possibility of food allergy (1).

As another example I should like to describe a patient which I have had under treatment since July, 1948:

This patient is a 27 year old white male who complained of recurrent abdominal discomfort, distention, nausea and vomiting since the age of nine years. An X-ray examination several months previously had apparently revealed a gastric ulcer and the patient was hospitalized and treated with a milk diet and ant-acids with resultant relief for a few days. However, when he returned to work, his symptoms recurred and were associated with repeated episodes of mild hematemesis. I tested the patient for food allergy by the scratch test and found a two plus positive reaction to cow and goat milk, cottonseed oil, and corn. There was a one plus positive reaction to chicken, rice, barley, spinach, peas, cantaloupe, lettuce, olives, eggs, tea, most fruits, wheat, and rye. The patient was placed on a diet which eliminated most of these foods. In addition, he was treated with sedatives, anti-spasmodics, Hapamine, and supplementary vitamins. His complaints subsided entirely within a few days, and his diet was gradually increased.

Starvation regimes, rice diets, and other rigorous routines may be successful in relieving some patients with gastrointestinal difficulties because they exclude possible allergenic foods. I have also had several patients whose gastrointestinal X-ray examination showed some abnormality (e. g. a peptic ulcer) and who exhibited positive reactions to scratch tests with food extracts. The use of Rowe's elimination diets in such patients often has brought quick relief even though the diet may have contained foods which ordinarily we would not use in the treatment of an active ulcer.

It must be remembered that skin reactions to food extracts are less reliable than those to extracts of inhalant allergens, and it is possible for a patient to tolerate without difficulty foods to which he may react positively on skin testing. Many patients have asymptomatic allergy, and I believe that such patients may remain asymptomatic unless there is an additive effect of several ingested allergens (or possibly combined with inhaled allergens) sufficient to excede the critical threshold of symptoms. Emotional upsets, fatigue, and menstruation may lower this critical threshold.

The physician must devote enough time to the patient to convince him of the importance of adhering rigidly to a diet which may eliminate some desired foods. (Wheat especially seems to be difficult for the average patient to relinquish). Often when the patient is on vacation, rested and contented, he may feel that the physician was too strict and therefore indulges in the forbidden foods. Usually, on this patient's return to work, however, his symptoms recur.

Patients are advised to eliminate allergenic foods for at least three months in the case of wheat and cottonseed allergies, and about two months for milk and the other allergenic foods.

Spastic constipation is a common concomitant of food allergy and proper attention must be paid to the establishment of normal bowel habits. Laxatives should be avoided for obvious reasons. I have found rectal suppositories to be helpful during the first few days after the patient has been placed on his special diet.

Any portion of the gastrointestinal tract could conceivably be disturbed by food allergy, and a wide variety of symptoms may result, suggesting intrinsic

General Abstracts Of Current Literature

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CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

COOK, T. J.: *Soft tissue lesions of the mouth.* (Bull. U. S. Army Med. Dept., Dec. 1948, Vol. VIII, No. 12, 944-949).

The dentist is likely to discover oral lesions highly diagnostic of general systemic diseases and among these the chancre, mucous patch and gummata of lues are important. Carcinoma, leukoplakia, lichen planus, the glossitis of pernicious anemia, necrotic stomatitis associated with agranulocytosis, gingival hypertrophy in leukemia, or in persons taking sodium diphenylhydantoine, and the gingival necrosis sometimes seen in uncontrolled diabetes mellitus, are among the lesions which the dentist may be the first person to examine.

STOMACH

REID, D. R. K.: *Perforation of gastric carcinoma.* (New Zealand Med. J., June 1948, Vol. 47, No. 259, 259-261).

The author describes a case of perforation of a pre-pyloric gastric cancer, correctly diagnosed clinically before operation, on whom suture and drainage was followed, six weeks later, by partial gastrectomy, life being prolonged about four months and the patient dying at home, presumably of secondary carcinoma. The perforation of a gastric cancer probably is not very rare, although comparatively few have been reported in the literature (250 up to 1946). There may be "acute" or "chronic" perforation. Prognosis for cure is hopeless as judged by statistics. The treatment of choice is immediate gastrectomy provided all facilities exist and the patient is sufficiently fit.

RIEKELES, G.: *Gastric syphilis.* (Nordisk Med., Aug. 13, 1948, Vol. 39, No. 33, 1503-1505).

A patient of 35 is described in whom indigestion led to a roentgen diagnosis of gastric malignancy but, on operation, an infiltrating inflammatory lesion was found with involvement of the lymph nodes. Postoperatively the Wassermann reaction was found to be strongly positive. Rapid improvement occurs in such cases on anti-luetic treatment. Sometimes surgery is needed for organic fibrotic obstructions which may develop. It should, of course, be remembered that ulcer and cancer of the stomach are much more common in syphilitics than is gastric lues.

FRIIS-HANSEN, B.: *Gastric secretion during fevers.* (Nordisk Med., Nov. 12, 1948, Vol. 40, No. 46, 2094-2096).

There is a prevailing belief that the dyspepsia associated with acute infections is due to lowered gastric acidity but the author, by investigating 12 patients and using the histamine test, found that gastric secretion was virtually normal. No gastroscopies were done, so that there is no report with respect to the presence or absence of gastritis.

PIRKEY, E. L. AND ROBERTS, S. M.: *Diagnosis of primary Hodgkin's Disease of the stomach.* (Radiology, Jan. 1949, Vol. 52, No. 1, 75-77).

Primary Hodgkin's disease of the stomach is rarely diagnosed. The literature records 22 cases and the authors present the 23rd case. The X-ray diagnosis in this case was infiltrating scirrhous carcinoma. Operation revealed Hodgkin's disease of the stomach with extension into the esophagus and perigastric lymph nodes. Operative cure of the condition is relatively high as compared with cancer and radiologists should keep this fact in mind whenever they diagnose infiltrating scirrhous carcinoma.

HENDERSON, A. T., HENDERSON, R. A. AND SPENCER, B. A.: *Congenital hypertrophic pyloric stenosis in mother and daughter.* (Archives of Pediatrics, December 1948, Vol. 65, No. 12, 654-656).

While congenital hypertrophic pyloric stenosis is relatively rare in females, eighty per cent occurring in males, the authors have found and studied the first recorded instance of the disease in mother and daughter, both of whom were cured by surgery. There are strong arguments for the existence of a genetic factor.

BOWEL

OGILVIE, H.: *Large-intestine colic due to sympathetic deprivation.* (Brit. Med. J., Oct. 9, 1948, 671-673).

Two cases are described in which increasing constipation, amounting to clinical obstruction, associated with painful spasms of the colon in the left lower quadrant, was present without the slightest radiographic evidence of obstruction or any other lesion in the colon. In each case operation eventually was performed and while no colonic lesion was found, there was malignant infiltration of the left crus of

the diaphragm in one case, and in the other, masses of malignant tissue of uncertain origin were encountered in the subdiaphragmatic region involving all the upper aortic glands, the celiac axis, and even the falciform ligament. Probably the subdiaphragmatic growth had interrupted the sympathetic supply to the large intestine, so that the parasympathetic innervation was allowed to act unopposed and thus caused the colonic spasm. The author regards this as a new clinical syndrome.

COLEMAN, J. M.: *Congenital fibrous bands at the anorectal line.* (Texas State J. M., October 1948, Vol. 44, No. 6, 454-457).

Among 1,000 children under one year of age an incidence of rectal pathological conditions was found in 9.3 per cent. Fibrous bands at the ano-rectal junction were the most frequent finding. The fibrous band is cured by careful digital dilatation. Its cure frequently assists in the control of associated "colic" and constipation.

BEEKE, V. G.: *Leiomyomata of the jejunum: report of a case associated with von Recklinghausen's disease.* (Harper Hosp. Bull., Sept.-Oct. 1948, Vol. 6, No. 5, 129-135).

A case is reported of a woman of 62 who presented recurring exacerbations of epigastric pain, tarry stools, anemia, with weight loss and debility, but in whom repeated X-ray studies failed to reveal the presence of multiple leiomyomata of the jejunum. Post-mortem examination showed these subserous tumors to be benign. She also presented neurofibromas of the skin. Obstructive symptoms resulted from the presence of the leiomyomata and such tumors, though rare, should be kept in mind as possible causes of intestinal bleeding.

NANSON, E.: *Multiple primary colonic malignancy.* (Proc. Roy. Soc. Med., Oct. 1948, Vol. 41, No. 10, 656-657).

A woman of 56, who 15 years previously had had a partial colonic resection for colonic cancer, presented malaise and a rectal hemorrhage of bright red blood. Barium enema revealed a definite filling defect in the pelvic colon. At operation, two quite distinct cancers, three inches apart, were found in the sigmoid and successfully dealt with surgically. It is of interest that, in this woman, who in 15 years had developed three primary colonic cancers, no evidence of polyposis existed.

ROBINSON, G. L.: *Hodgkin's disease confined to the jejunum.* (Brit. Med. J., Nov. 6, 1948, 822-823).

A man, aged 51, was admitted to hospital complaining of post-prandial epigastric burning. X-ray examination revealed a filling defect in the colon which, at operation, was found to be due to adhesions between the jejunum and colon. The wall of the excised piece of jejunum, the adjacent mesentery and some neighboring lymph nodes showed characteristic histology of Hodgkins' disease. The patient died on the 15th post-operative day of peritonitis. Only about 30 cases of Hodgkin's disease affecting only the gastro-intestinal tract have thus far been described.

ARENDT, JULIAN AND COHEN, JACK: *Mucosal studies in colitis due to parasites.* (Am. J. Roent. Rad. Therapy, 59, 6, 805, June 1948).

The authors studied 32 cases of parasitic infection of the colon. In a high percentage of these cases, mucosal changes, such as spider-like widening and derangements of the folds, were found in typical localizations, particularly in the cecum pole, ascending colon and sigmoid. Increased sparsity was observed in these areas, in combination with mucosal changes sometimes taking the form of the previously described cone-shaped cecum pole. Not only were but also milder types of Endamoeba histolytica infections and one case of Dientamoeba fragilis and of Monilia invasion showed deviations from the normal.

Changes in the cecal area and lower ascending colon combined with deviations from the normal in the sigmoid are strongly suggestive of protozoan infection. Continuous involvement of the colon ascending from the rectum and sigmoid suggests ulcerative colitis. The character of the various ulcerations provides another point of differentiation. The demonstration of amebic ulcerations in the cecum pole is rarely possible. FRANZ J. LUST

OWEN, R. A. C.: *Intussusception in adults due to carcinoma of the colon.* (Brit. Med. J., Oct. 30, 1948, 786).

The author gives detailed reports on two cases of that excessively rare entity — colonic intussusception due to cancer. Only 30 other cases can be found in the literature.

MESSAROVI, J. E. AND MORLOCK, C. G.: *Mesenteric vascular occlusion.* (Proc. Staff Meet., Mayo Clin., Nov. 10, 1948, Vol. 23, No. 23, 521-527).

A case is described in which operation undertaken for abdominal pain of uncertain etiology, revealed a 12 inch portion of the small bowel affected by occlusion of an ileac branch of the superior mesenteric artery. Since this portion of bowel was bright pink and appeared viable, it was not removed and the patient made a good recovery. He had previously had two attacks of coronary thrombosis. The authors emphasize that the symptoms of mesenteric vascular occlusion are those of acute intestinal obstruction, strangulation of the intestine, rupture of a viscus, or peritonitis.

GRAY, H. K. AND LOFGREN, K. A.: *Lymphosarcoma of the small intestine.* (Proc. Staff Meet. Mayo Clin., Nov. 10, 1948, Vol. 23, No. 23, 538-542).

A case is described in which a lymphosarcoma involving the entire circumference of the bowel was found in the mid-portion of the ileum and removed. Roentgen-ray therapy was applied to the abdomen post-operatively. The authors point out that lymphosarcomata are extremely sensitive to X-rays. The chief symptoms were intermittent vomiting and cramping pains in the abdomen. X-ray studies before operation gave no evidence of the lesion.

ESTREM, T. D.: *Regional enteritis.* (Journal Lancet, Nov. 1948, Vol. 68, No. 11, 417-422).

The author reviews the important literature on regional ileitis and indicates that medical treatment alone is indicated in only a few selected cases. In recent years there is a trend to abandon resection of the diseased bowel in favor of the short-circuiting ileo-colostomy with exclusion.

ZEISSLER, J. AND RASSFELD-STERNBERG, L.: *Enteritis necroticans due to clostridium welchii type F.,* (Brit. Med. J., Feb. 12, 1949, 267-269).

This is an extremely important paper, because it not only fixes enteritis necroticans as a clinical entity, but also proves that the associated microorganism is a hitherto unrecognized strain of B. welchii, viz., clostridium welchii Type F. Clinically the disease consists of a somewhat fulminating inflammation of the small and large bowel producing diffuse sloughing. The most severe lesions are tube-like areas of necrosed mucosa a foot or more in length. The disease presumably is rapidly fatal and characterized by very severe abdominal pain, vomiting, and profuse diarrhea with marked dehydration, leading in a few days to circulatory collapse with cyanosis. The organism invariably isolated, differs from B. welchii types A, B, C, D, and E, in that it forms different types of colonies on blood agar, and morphologically shows a much more elongated form and even chains of spindles. The spores of this strain resist boiling, often for four hours, whereas the spores of other types are killed by 15 minutes boiling. This renders its isolation comparatively easy. The main toxin produced is beta toxin, consequently treatment with Cl. welchii type A serum would be of no value as this serum contains no beta toxin. Sulphadiazine does not affect the growth of Type F at all. *In vitro* tests showed it was inhibited by 10 units, but not by one unit of penicillin per ml. It is sensitive to sulphanilylthiourea and extremely sensitive to sulphamylon.

WYATT, GEORGE M.: *Barium sulfate in saline suspension. — Examination of the colon in the presence of partial obstruction.* (Radiology 51, 3, 326. September, 1948).

There is a small group of patients with symptoms of unexplained rectal bleeding or abdominal tumor who present an unusually difficult diagnostic problem to the roentgenologist. These patients fall into two categories:

1. The patient who cannot retain an enema because of a relaxed or damaged anal sphincter or perineum.

2. Patients who do not have clinical obstruction or dilatation of the intestine but who present complete obstruction to the retrograde passage of a barium enema. It is with this group of patients that this paper is primarily concerned. Many of these patients have diverticulitis, and a small percentage also have a rectal bleeding due to diverticulitis.

Oral administration of barium in the presence of obstruction of the lower bowel is considered dangerous because of the probability of dehydration and impaction. Even normal patients often have difficulty in expelling the barium. One logical method of preventing dehydration of the barium is to administer it with a saline cathartic which, by its nature, maintains and increases liquefaction of the contents of the colon. The authors method is to have the patient hospitalized. Four ounces of barium is mixed with eight oz. of magnesium citratis. This mixture is given orally early in the morning and the patient is allowed water ad lib. Another eight oz. of magnesium citrate, without additional barium is given about an hour and a half later, and fluoroscopy is then done at intervals starting about two hours following the administration of the barium. The speed of the passage of the barium-saline mixture varies markedly with the degree of obstruction and the age and physical activity of the patient. Excretion is usually almost complete at the end of eighteen hours or earlier. Such patients must obviously be kept under roentgenological observation until the barium is excreted and should be kept in the hospital for facilitation of such observation.

Excellent roentgenograms demonstrating cases of neoplasms and diverticulitis illustrate the author's method. FRANZ J. LUST, M.D.

COLON

PENDERGRASS, ROBERT C.: *Extrinsic deformities of the colon.* (Radiology 51, 3, 320. Sept. 1948).

Extrinsic deformities of the colon may be roughly grouped as follows:

1. Deformities from enlarged viscera, including tumors of these viscera.

2. Deformities from inflammatory processes, adhesions and endometriosis.

3. Deformities from retroperitoneal tumors, mesenteric tumors, and omental tumors.

4. Deformities from tumors of the colonic wall not invading the mucosa.

5. Deformity from intra-abdominal and inguinal hernia. Instructive roentgenograms accompany this article. There are cases of: depression of the hepatic flexure by carcinoma of the kidney, aspect of the colon before and after drainage of a perirenal abscess, appendiceal abscess, leiomyosarcoma of the

colonic wall, ileo-cecal tube, internal hernia simulating displacement by intra-abdominal masses.

FRANZ J. LUST, M.D.

PANCREAS

ROSE, T. F.: *Spontaneous rupture of a pancreatic pseudocyst.* (Med. J. Australia, Sept. 4, 1948, 258-259).

A case is reported of a man, 31 years old, who had always been well but, three days before admission to hospital, noted upper abdominal swelling of a degree which interfered with the fit of his clothes. This swelling was accompanied by a constant aching pain. It lasted for two days, when the distention suddenly disappeared, followed by epigastric pain of ever-increasing intensity, and board-like muscular rigidity. On abdominal exploration a quart and a half of coffee-like fluid was found, but there was no fat necrosis. A pancreatic pseudocyst, of grapefruit size, had ruptured through the greater omentum just below the greater curvature of the stomach, and this was drained by a rubber tube. He made a good recovery. The drainage lasted 10 days. The pseudocyst may have resulted from previous pancreatitis.

HEWLETT, H. M.: *Carcinoma of the duodenum.* (Med. J. Australia, Oct. 30, 1948, Vol. 35, No. 18, 517-518).

The author made a diagnosis of carcinoma of the duodenum in a woman of 57, by means of an X-ray deformity of the duodenum involving a portion of the greater curvature of the stomach. This was considered, without doubt, to be an example of that rarity — primary cancer of the duodenum. Because of the delay in operation, it had had time to extend into the stomach. The author himself confesses never to have seen it before in records of over 40,000 opaque meal examinations. Usually cancer of the duodenum is a direct extension from a carcinoma of the head of the pancreas.

DE LANGE, C. AND JANSSEN, T. A. E.: *Large solitary pancreatic cyst and other developmental errors in a premature infant.* (Am. J. Dis. Child., April 1948, Vol. 75, No. 4).

The case of a child with a large solitary cyst of the pancreas and several other developmental errors is reported. The child died of pneumonia when one week old. When a child presents symptoms of vomiting, constipation and pain and if a mobile tumor is felt in the abdomen, we must consider cyst of the pancreas, ovary or mesentery, or hydronephrosis. A fluoroscopic study after an opaque meal may be very useful in determining the size of the tumor. Operation frequently is life saving.

LOWELL S. GOIN: *Fibrocystic disease of the pancreas.* (Radiology 51, 1, 36. July, 1948).

Fibrocystic pancreatic disease is a congenital, familial, highly fatal disease of infants, regularly accompanied by pulmonary changes which are demonstrable in the roentgenogram. The disease has become recognized as a clinical entity only in the past ten years due almost entirely to the work of Dorothy Andersen. The cause of the disease remains unknown. The histopathologic factor is that of obstruction of the smaller pancreatic ducts and subsequent dilatation of the acini. There is a severe vitamin A deficiency. The lung changes are the basis of the roentgenological findings. There are bilateral hilar densities, with mottled linear densities extending outward, marking a set of arcs about the cardiovascular shadow. Bronchopneumonic patches are seen, and a honeycomb appearance of the lung leaves frequently represents bronchiectasis. The bronchopneumonic areas may be quite extensive, and bronchopneumonia is commonly the immediate cause of death. The symptoms and clinical findings are those of gross deficiency of pancreatic secretion. The stools are bulky, foul and gray, the abdomen is distended. The fat contents of the stools is 60%, there is a delayed glucose absorption and a poor vitamin A absorption. Diarrhea and repeated respiratory infections develop. Vitamin A up to 150,000 units per week and casein hydrolysates instead of milk, should be given.

FRANZ J. LUST, M.D.

REEVES, ROLLIN J. AND MORAN, FRANK T.: *Diffuse pancreatic calcification.* (Radiology 51, 2, 219. August 1948).

The authors describe the case of a four year old child with diffuse pancreatic calcification, apparently the earliest case on record. Besides, five other cases, all under 35 years of age are reported, all of them had severe complaints for two to eight years. The child had never had abdominal pains. Two patients gave a history of excessive alcohol consumption. Four cases had diabetes mellitus. Serum amylase was increased in one case. The roentgenologic finding of calcium within the pancreatic parenchyma is of considerable significance. Since it becomes deposited in areas of fat necrosis, fibrosis, or degenerative tissue, it indicates the site of a pathologic process. Two cases had pancreatic achylia. Due to the pains, one case bordered on drug addiction, another had such intractable pains, that bilateral ganglionectomy had to be performed.

FRANZ J. LUST, M.D.

ULCER

EDLEN, A.: *Ulcer and ulcer treatment.* (Nordisk Med., July 16, 1948, Vol. 39, No. 29, 1344-1348).

The author finds functional disorder of the liver to be a part of the peptic ulcer syndrome, important enough as to serve in helping make a diagnosis of ulcer. He believes the hepatic dysfunction precedes the development of the ulcer. He feels that emotional disturbances are among the trigger mechanisms in the etiology and therefore emotional rest is important in treatment. He also recommends the use of ergotamine and dihydroergotamine in treatment of ulcer.

MEULENGRACHT, E.: *Analysis of fatal cases of bleeding peptic ulcer treated with free and frequent feedings.* (Nordisk Med., Aug. 13, 1948, Vol. 39, No. 33, 1490-1495).

The author has used free-feeding in bleeding peptic ulcer for 15 years, routinely, on 1031 cases of whom 26 terminated fatally while in the hospital. All but one of those who died were over 40 years of age. In all fatal cases vomiting of blood occurred. If cases are excluded in which death was due to causes other than hemorrhage and also those who died 24 hours after admission, the mortality was only 1.5 per cent. The author advises more liberal use of blood transfusions in cases that threaten to terminate fatally. In only a *very* small group should operation be undertaken to control bleeding.

COLP, RALPH: *Surgical treatment of gastric, duodenal and gastrojejunal ulcer, including the present status of vagotomy.* (Bull. New York Acad. Med. Second series, Vol. 24, 12, 755, December, 1948).

Vagotomy as a sole procedure has been abandoned in the treatment of unobstructed duodenal ulcer as a result of Colp's experiences in a series of twenty-one cases, because seven of them required further surgery, two for recurrent duodenal ulcer, and five for gastric dilatation and atony. The completeness of the division of the vagi as evidenced by the insulin test bears no relationship to the clinical results. The addition of gastroenterostomy to vagotomy seems to have eliminated the undesirable effects of gastric atony in 26 cases of duodenal ulcer in which it was performed. Whether the incidence of gastrojejunal ulceration will be lessened by the combination of vagotomy and gastroenterostomy, as compared to gastroenterostomy alone, only long range follow-up studies will determine. Gastroenterostomy combined with bilateral infradiaphragmatic vagotomy is the preferred procedure in cases of duodenal ulcer unsuitable for subtotal gastrectomy.

For Colp the subtotal gastrectomy still remains the operation of choice in duodenal ulcer. It has been combined with infradiaphragmatic vagotomy in a series of patients whose preoperative acidity was high, and who had a tendency to bleed. There has been no increase in the operative mortality and a slight increase in the postoperative morbidity attributable to the added vagotomy. Whether the incidence of recurrent gastrojejunal ulceration will be diminished remains a subject for further study.

The immediate results of vagotomy in the treatment of gastrojejunal ulceration following gastroenterostomy and subtotal gastrectomy have been excellent. Subsequent follow-up has revealed recurrent ulceration in some cases. In patients considered to be good operative risks, a subtotal gastrectomy with infradiaphragmatic vagotomy is preferable to vagotomy alone for gastrojejunal ulceration following gastroenterostomy. In gastrojejunal ulceration following subtotal gastrectomy, wherever possible resection of the ulcer and further gastric resection combined with infradiaphragmatic vagotomy would seem preferable to the severance of the vagus nerves alone.

Vagotomy is not indicated in the treatment of gastric ulcer. FRANZ J. LUST, M.D.

BOWEL

DUNDON, CARROLL C.: *Primary tumors of the small intestines.* (Am. J. Roentgen. and Rad. Th. 59, 4, 492. April, 1948).

Sixty-two cases of tumors of the small intestine were collected from the records of the University Hospital of Cleveland in a period of 13 years. There were 44 benign tumors of which only two caused symptoms. These were cases of intussusception produced by pedunculated tumors — 18 malignant tumors were recorded and 12 of these cases were carcinomas. Five of the carcinomas were in the jejunum, four were in the ileum, and three were in the duodenum. There were two lymphosarcomas, both in the jejunum. The other malignant tumors were one leiomyosarcoma of the jejunum, one fibrosarcoma, and two malignant carcinoids of the ileum. The chief symptoms of the malignant tumors were abdominal pain, vomiting, diarrhea and weakness. Seven of the twelve cases of carcinoma had abdominal pain for an average of seven months. The tumor was palpable in nine of 18 cases. There were no signs or symptoms in five cases.

Roentgenographic examination showed evidence of a lesion of the small intestine, upon review of the roentgenograms, in eight of 11 cases which were examined. The diagnosis of primary tumor of the small intestine was made twice, and the possibility of that condition was mentioned in three additional instances. Eight patients who had barium studies showed the intestine to be dilated by the lesion in one case, irregular narrowing of the intestine in four cases, complete obstruction to the passage of barium in two cases, and marked hypermotility in one case. Ten out of twelve operated cases had metastasis or local extension of the tumors to adjacent abdominal organs.

Carcinoma of the small intestine characteristically causes an irregular constriction of the bowel, two to six cm. in length, with a tortuous column of barium through the lesion. Lymphosarcomas can occasionally be identified because the lumen of the tumor is larger than the normal intestine. There is a group of malignant tumors, which defies diagnosis. These cases do not give a typical history, cause no obstruction or bleeding and no abdominal mass can be palpated. FRANZ J. LUST, M.D.

SWENSON, PAUL C. AND WIGH, RUSSELL: *The role of the roentgenologist in the diagnosis of polypoid disease of the colon.* (Am. J. Roent. and Rad. Therapy. 59, 1, 10. January, 1948).

Roentgenograms and some pathologic reproductions together with case histories have been pre-

sented illustrating four classes of polypoid disease of the colon, namely: the single lesion, the limited but multiple type, true multiple polyposis, and the polypoid manifestations in ulcerative colitis. These cases were grouped clinically as they presented themselves to the roentgenologist. The single contrast study, the double contrast study (with stereoscopy), and the roentgenoscopically controlled compression study have all been demonstrated. Pedicles and dimpling of the bowel wall at the site of attachment of the pedicle or of the mass itself have been demonstrated and discussed in reference both to diagnostic and surgical importance. Suggestions have been made to aid in the selection of one or more methods of roentgen study.

The authors show very interesting roentgenograms of cases of nonspecific ulcerative colitis. In each case severe diarrhea and bloody stools were the chief complaints and the proctosigmoidoscopic examination revealed changes characteristic of ulcerative colitis. The roentgenograms chosen show those changes which simulate multiple polyposis. There are two principal features. One is that of islands of mucosa, either normal or edematous, which project into the bowel lumen between ulcers and although they present a polypoid appearance are merely pseudopolyps. The second feature is actual polypoid formation, resulting from the piling up of mucosal shreds. Contributory roentgen evidence, particularly loss of haustrations and narrowing of the bowel lumen, should permit the differentiation from the familial type of multiple polyposis. FRANZ J. LUST, M.D.

LIVER AND GALLBLADDER

GRAY, H. K., DUSHANE, J. W. AND HENEGAR, G. C.: *Cholecystogastrostomy for congenital atresia of the common bile duct.* (Proc. Staff Meet. Mayo Clinic, Oct. 13, 1948, Vol. 23, No. 21).

The two cases reported represent two of the very few cases of congenital atresia of the common bile duct in which surgery has been of benefit. In 12 other cases, surgery produced no benefit. In the two successful cases the gall-bladder was anastomosed to the anterior wall of the pyloric antrum. Bile appeared in the stools on the fifth post-operative day. Both patients are apparently progressing satisfactorily.

PETERSON, V. P.: *Hemochromatosis and primary carcinoma of the liver.* (Nordisk Med., Dec. 3, 1948, Vol. 40, No. 49, 2262-2264).

A case of hemochromatosis in a 45 year old man is described. In spite of considerable hepatic enlargement during the past five years of his life, various liver function tests did not suggest severe liver damage until late in the disease. Histological examination of autopsy material revealed a diffuse cancer of the liver derived from the bile ducts and metastasizing to the lung.

MAYO, C. W., AND RICE, R. G.: *Cholecystitis and cholelithiasis with complete situs inversus viscerum.* (Proc. Staff Meet. Mayo Clin., Dec. 22, 1948, Vol. 23, No. 26, 610-611).

Previous to the report of this case, only 19 instances have been recorded in the literature of gall bladder inflammation and gall stones occurring in patients with complete situs inversus viscerum. At the Mayo Clinic only two such cases have been subjected to surgery. In the case under discussion the symptoms apparently did not differ in any particular way from those which usually are described by the anatomically normal individual.

STOMACH

BAILEY, W. H.: *Gastric surgery with special reference to peptic ulcer.* (Med. J. Australia, Feb. 7, 1948, Vol. 35, No. 6, 167-171).

When medical measures fail in peptic ulcer, a partial gastrectomy of adequate dimensions is desirable. He feels that in younger patients with pyloric obstruction, gastro-enterostomy is the treatment of choice. He favors operation in cases of very severe hemorrhage from ulcer or in cases where smaller hemorrhages have occurred more than twice. In acute perforation he favors early operation and suture. He does not believe that "physiological" gastrectomy (ligation of three-quarters to five-sixths of the arteries of the stomach) has proved its value. He regards vagotomy as being still under trial.

The Phenomenon of Peptic Ulcer

By

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THE CAUSE OF ULCER IS UNKNOWN. Clinical, pathological and laboratory investigations on peptic ulcer go back 150 years. The accumulation of observations is tremendous. A number of theories on the etiology of peptic ulcer have been brought forward, but none of them has been definitely proven. It seems to the speaker that this is a good time and a good place for a critical review of some of the known and established facts and of the more probable theories.

The question of peptic ulcer can be put this way: why does an ulcer form in a predilected area of the stomach (lesser curvature, pre-pyloric) or of the upper duodenum? We know that acute ulcers heal rapidly, naturally or under experimental conditions. Thus the second question arises, what makes an ulcer chronic?

The protagonists of the acid theory of peptic ulcer maintain, that more or less constant relative hyperacidity and hypersecretion break down the resistance of gastric or duodenal mucosa and cause not only the ulcer but also its chronicity. This view brings us back to the oldest question connected with peptic ulcer, namely, why do stomach and intestine not digest themselves? Obviously, if this would be as simple as peptic digestion, the entire stomach and small intestine should be digested. The trouble is, that too little attention is paid to the typical localization of most peptic ulcers. Obviously, a locus minoris resistentiae must exist before digestion can occur, in other words, a devitalized area must exist first.

What makes a small area of stomach or duodenum, localized near the pylorus or in the duodenal bulb, devitalized or at least, what makes its resistance to digestion break down? The most plausible answer seems to be the occurrence of vascular changes in the stomach.

Vasoconstriction undoubtedly occurs in the normal stomach. Blanching of the mucosa and serosa have been observed during periods of anger, fear and, to a lesser degree, during inactivity. However, the formation of erosions and bleeding and ulceration have been observed only when the mucosa was engorged, and when acid secretion and motility were quite active (suppressed resentment, 1, p. 222). There is no proof however, that such ulcers ever become chronic. Wolf and Wolff have ascribed the formation of acute ulcers to lack of mucus protection of the gastric mucosa, and have inferred that depression of mucus secretion is a cause of chronic peptic ulcer (1, p. 222). A localized depression of mucus secretion brings us back to localized damage to cells, probably by anoxemia, the latter due most likely to stasis or to vasoconstriction. Concerning secretion of mucus by the whole stomach, no difference has been found between normal persons and ulcer patients, using an improved quantitative method (2).

Can the formation and typical localization of ulcer be explained by focal vasoconstriction or spasm? The stomach is one of the most vascular organs of the body; most of its arteries can be ligated with impunity (3). Yet, when embolism is produced in small arteries, ulcers form (4); likewise, in animals that receive histamine in beeswax injections, acute ulcers form when fat embolism is produced, a procedure which did not evoke ulcer in control dogs (5). End-arteries have been found in the pyloric antrum, on the lesser curvature, and in the duodenal bulb (6-8). If an end-artery is obstructed physically or functionally, necrosis of the area supplied by it develops, because collateral blood supply is inadequate. Such mechanism can explain satisfactorily the higher incidence of peptic ulcer in diseases in which embolism is known to occur, such as following operations, in poly cythemia vera, after burns, etc., possibly also in marantic, bedridden patients. However, these conditions can explain only a relatively small percentage of peptic ulcers, and these are acute or subacute. What then can create an anoxemic area in the stomach of an otherwise normal person? We believe that the vagus-acetylcholine mechanism may be responsible. Dale and Feldberg, (9) have found that following vagus stimulation a distinct increase of acetylcholine occurred in gastric venous blood of eserinerized animals. We have tested the effects of such small concentrations of acetylcholine as found by Dale and Feldberg on the rate of perfusion, on the bloodflow and on the blood vessels of the stomach of the rat, the dog, and the human (9, 10). The isolated rat's stomach was perfused with oxygenated saline or Ringer's solution. Acetylcholine produced a reduction of flow up to 44%. The dog's stomach was prepared in situ, so that the rate of venous return into the splenic vein could be measured, or it was transplanted into the neck of the dog, where arterial and venous flow were measured. Acetylcholine produced a reduction of venous flow between 31 and 96%. Blood vessels from human stomachs were secured in the operating rooms and were perfused immediately in the laboratory. Acetylcholine produced a marked reduction in the flow of the perfusion. As control, the rate of perfusion was measured in the leg of the rat and in the rabbit's ear, and the rate of bloodflow was determined in the leg of the dog; injection

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of acetylcholine was followed always by increased venous return.

From these results we concluded, that acetylcholine acts on the blood vessels of the stomach differently than on the blood vessels of the leg and ear contracting the former and dilating the latter. In further work it was found that gastric juice contains acetylcholine and that following stimulation, particularly with histamine, the acetylcholine concentration increases (11).

The vagi are the main secretory and motor nerves to the stomach. Acetylcholine and other choline esters, as well as prostigmine, increase gastric secretion and motility (12). It is assumed, that vagus effects on the stomach are mediated by acetylcholine. It is clear that in a highly vascular organ like the stomach reductions in blood flow can produce localized hypo- or anoxemia only in regions of end-arteries, where collateral blood supply is inadequate. Such areas are those of the prepyloric lesser curvature and of the upper duodenum, areas in which most of the typical peptic ulcers occur. Now, it is established fairly well, that in ulcer patients, at least in the patient with duodenal ulcer, there is not only increased but apparently constant vagus activity, as manifested by hypermotility (we found this to persist even after subtotal resection for duodenal ulcer, 13), and by hypersecretion, the latter persisting during the night. Thus, to come back to the areas with end-arteries, it is conceivable, that continuous vagus activity produces constant liberation of acetylcholine, the latter producing continuous vasoconstriction, followed by hypo-or-anoxia of the tissues in these areas. It has been demonstrated that during anoxia the gastric mucosa needs glucose, and that without O_2 or without glucose, the mucosa disintegrates rapidly (14). From the above we can deduct that permanent vagus activity may lead to an acute ulcer. Such ulcer, under the continuous effects of vagus activity, may become chronic (10).

From the above statements it appears that HCl and pepsin are not prerequisites for the development of peptic ulcer. I realize that such an opinion opposes many outstanding workers in this field, but I feel that it merits consideration.

The following observations are considered to argue against the acid theory of peptic ulcer (no acid, no ulcer): Ulcers are found in the esophagus, lower duodenum, jejunum, ileum, and colon, without relation to a degree of acidity which would permit digestion. Reports are available on duodenal ulcers in diabetics with low acidity or with histamine refractory anacidity (15). High acidity is found frequently in persons without ulcer, low acidity in patients with ulcer. We have observed quite a few times that healing of ulcer was accompanied by increased acidity. We have seen duodenal ulcer preceded by low gastric acidity, as shown by our findings in normal relatives of ulcer patients, many of whom came into our care later as patients with peptic ulcer (16). Peptic ulcer has been observed to heal even when treated with histamine injections or with administration of acid by mouth (17). Quite a few cases of excellent clinical cures are on record in patients with vagotomy, in the presence of unchanged high acid secretion (complete or incomplete vagus section, 18).

Most peptic ulcers are in the duodenum. The pH in the duodenum is about 6.5; at times it is lower, but only for minutes, even in ulcer patients. At pH 3.5 there is little peptic activity, at pH 5 none. The neutralizing mechanisms of pancreatic and bile secretions have been found to be normal in duodenal ulcer patients.

Why then the dictum "no acid, no ulcer?" Because peptic ulcer occurs in the stomach and because the stomach secretes acid, the two ideas have been put together by force of illogic. The idea would be more reasonable, if 90% of peptic ulcers would occur in the stomach rather than in the duodenum. Fifty years ago most peptic ulcers were in the stomach. At that time the acid-pepsin theory was on a better basis than nowadays. Normal gastric acidity apparently does not affect a normal stomach. All experiments in which corrosions in the stomach or intestines were produced, were done with unphysiological concentrations of acid and under highly abnormal conditions. If the above dictum would say "no *hyper*-acidity, no ulcer," it would come nearer the truth, although not quite. Many of us in this hall have hyperacidity and, I am sure, quite an acid night secretion, and have no ulcer.

How much acid does it take to form an ulcer? In many patients very little. Acid secretion is within normal range in about half of all patients with duodenal ulcer; and it is normal or below normal in most patients with gastric ulcer. Tests for gastric acidity have been found to be an unreliable index for the diagnosis of peptic ulcer, and have been given up as a routine test by the army and navy and by many clinics in this country and abroad. We have tested gastric and intestinal mucosa from various sites for its digestibility in HCl of pH 1.5-2 with and without pepsin, and in alkali with and without trypsin. Gastric and intestinal mucosa dissolved nearly as quickly in pure HCl as in HCl pepsin, and in pure bicarbonate as in bicarbonate trypsin (unpublished results).

Thus, pepsin need not be a prerequisite for the formation of peptic ulcer. Dead cells of gastric and duodenal mucosa seem to possess enough intracellular enzymes for digestion at acid or at alkaline pH. I can go even further than that: dead cells liquefy in an aqueous medium at any pH observed in the body.

Here I want to mention the famous experiment of Claude Bernard, namely the digestion of the leg of a living frog. This occurred only in acid pepsin, not in alkaline trypsin, and was confirmed by many. We have extended these experiments and found that, when a frog's leg was exposed to HCl-pepsin solution of a pH of 1.5 until slight digestion had occurred, and then to alkaline trypsin solution, digestion pro-

ceded. When a leg was exposed to HCl only, or to HCl-pepsin for such a short period of time that no visible digestion could take place, and then was placed in alkaline trypsin solution, digestion occurred. We expained this finding by assuming a corroding effect of HCl on the superficial protecting layers of the skin and subsequent digestion by pepsin or trypsin. We felt at that time, that the greater frequency of duodenal ulcer may be explained by alternating exposure to pepsin and trypsin (19). We did not observe a change in the pH of the blood during digestion (20).

What facts are in favor of the acid theory of peptic ulcer? Here one can quote the incidence of peptic ulcer following ligation of the bile or of the pancreatic ducts, the Mann-Williamson operation, the histamine in beeswax ulcer, and the prevention of most of these ulcers by surgery. The latter either decreases the size of the acid secreting areas of the stomach, or re-implants the transposed bile and or pancreatic ducts (Mann-Williamson operation) at or near their natural locations, and thereby prevents formation or produces healing of ulcers. Now, in criticism it must be said, that all of these ulcers are acute, and that they occur only in animals in which nutrition is deficient, and where gastro-intestinal motility, digestion, and absorption are interfered with severely. Concerning the beeswax-histamine ulcer it can be said, that the severe toxic effects, which kill a number of animals before ulcer develops, can explain ulcer formation, because in many experiments with shock and with a wide variety of poisons, acute ulcers are known to occur frequently. In approximately 10,000 autopsies on dogs I have not seen a chronic peptic ulcer in a normal healthy animal. I believed once I had found one, but on dissection it was found that a nail was glued by omentum to the serosa opposite the ulcer; apparently, after a nail had been swallowed, it had perforated the anterior gastric wall and had been fixed to the stomach by omentum. The irritation apparently had kept the ulcer in a chronic state. Acute ulcers in the dog we have seen many, but all these animals were sick, debilitated, and deficient in nutrition. The same seems to occur in man, where acute perforating ulcers are seen following operations, wasting disease, brain tumor, and in children with meningitis. Whether the ulcers seen in connection with brain tumors are due to disturbances in the brain, particularly the midbrain, as assumed by Cushing and his school, or whether they are due to wasting and to increased protein catabolism, often fulminating, is a point which has been raised and waits for a definite answer (21, 22). In a number of cases with intracranial disorders no distinct punched out typical ulcers were found, but softening of large areas of the stomach, possibly agonal.

Another weighty argument in favor of the acid theory is the effect of antacids in the prevention or the healing of peptic ulcer in man or in the experimental animal, and the recurrence of the ulcer in the Mann-Williamson dog following termination of such medication. With antacid therapy we neutralize gastric acidity for short periods of time only; for instance , in man we found that two grams of sodium bicarbonate in water by mouth depressed gastric acidity for only 10 minutes. Then acid secretion was as high as before, eventually even higher when "rebound" of acid secretion occurred. Yet, the ulcer patient often has relief from his pain for several hours.

I omit discussing enterogastrone or urogastrone in the prevention or healing of ulcers in view of our own findings with small doses of pyrogens which do not raise body temperature, but which have similar effects on the stomach as uro- or enterogastrone; both of the latter substances may contain subpyretic amounts of pyrogen (23, 24). Furthermore, the specificity of the mechanism of uro- and enterogastrone has been opened widely by the recent findings of Ivy's group, that enterogastrone is ineffective in preventing ulcer in the vagotomized animal (25).

One observation which seems to be important is, that psychic disturbances may produce an ulcer, that they may aggravate an existing ulcer, or that they may incite the recurrence of a healed peptic ulcer, and that they may bring about dangerous complications.

How then can we bring these opposing facts together and explain peptic ulcer?

Most alkalis seem to affect motility more than acidity. They relax the pylorus, the pyloric antrum, and the first part of the duodenum, and they enhance gastric emptying (26-31). The effects of drugs on the blood-flow through the stomach and duodenum is not known. Concerning food, Beaumont has observed increased vascularity of the stomach with meals ("on the application of aliment the action of the vessels increased, the color brightened,") and Wolf and Wolff (1) have confirmed this. F. C. Mann and coll. have shown a considerable increase of blood flow in various areas of the body following a meal (41). An ulcer is surrounded by an area of congestion and edema, and increased bloodflow following a meal or following certain drugs may drain the edema and thereby alleviate pain. Edema of the submucosa of the gastro-intestinal tract is painful, particularly when waves of contraction pass over the area (26 29, 33). Spasmolytic drugs may act through diminution of tone, motility, or spasm. An acute ulcer, without much inflammatory reaction often is painless and may give no other indication of its presence than hemorrhage or perforation. Infiltrating hard carcinoma of the stomach is often accompanied by pain, fungating soft carcinoma often is not. Hemorrhage often relieves pain, probably by decongestion. Surgical operations remove the most muscular, most contractile part of the stomach, and aid in more rapid gastric evacuation; also they usually remove the ulcer areas of predilection, probably the areas with end-arteries.

If there are end-arteries where peptic ulcer usually occurs, these may contract under the influence of acetylcholine, and peptic ulcer may develop in devitalized areas in the presence of high acid pepsin, or with little or no acid-pepsin. It is possible however,

patients and normal subjects. No differences in volume of secretion between the groups at any time. The only statistically significant difference found, occurred at 10 and 20 minutes following the chewing of a chilled orange, and consisted in a 13 and 15 clinical units greater free acidity in the ulcer group, and no statistically significant difference between the values for total acidity. The peak for the ulcer and control groups were respectively: free acidity: 36 and 26, total acidity: 64 and 52: all within the range of normal acidity following an Ewald meal. The volumes secreted were small, and the duration of appetite secretion was short, about 20 minutes. Individual values varied widely; therefore, sham feeding cannot be recommended for diagnostic purposes. Moskowicz (38) hypothesized increased psychic secretion to be able to produce ulcer (deducted from dog experiments by Silbermann, which could not be confirmed by Fogelson, (39). Our findings corroborate the views of Majus and Porges (43), that psychic secretion is secondary in importance to the gastric phase of secretion. Seemingly, psychic secretion is much less in man than in the dog. The moderately higher acidity of appetite juice does not reach the values considered to be hyperacid, and does not warrant giving it a role in the pathogenesis of peptic ulcer.

At this point, we can come back to the role of atropine and similar drugs in peptic ulcer. Undoubtedly, atropine has a beneficial effect on the distress of a number of patients with peptic ulcer. However, it is realized more and more, that the effect of atropine on volume and acidity of secretion in the normal subject and in the ulcer patient is so small, that it is often doubtful. On the other hand there is agreement that atropine, Trasentin and similar drugs, lower gastric tone and motility. Besides this, atropine has been found by my group to counteract the vasoconstrictor effects of acetylcholine on the stomach. In the light of my theory, atropine, Trasentin and similar drugs; would be more ideal agents than vagotomy, if we could make their action more or less continuous; this work is being done.

SUMMARY

The phenomenon of peptic ulcer is not a local one, and the importance of hyperacidity has been overemphasized. Peptic ulcer is an acute lesion which becomes chronic in most cases in two small circumscribed areas. If it would be only for acidity, ulcerations should be in all areas of acid secretion and mainly in the stomach. We have to think of a disturbance which first localizes and produces death of cells, like constant nerve activity in areas of end-arteries; such a focus of irritation and inflammatory reaction may well produce the increased acid and night secretion in ulcer patients as a secondary effect. Studies on psychosomatic causation of hypersecretion and loss of mucus protection with consequent ulcer formation are just a few and without controls.

If anxiety is removed in psychiatric cases by lobotomy, anacidity or subacidity is changed into normo- or hyperacidity, but no ulcers have been observed (40). Concerning the constitutional ulcer type, there is quite a disagreement between Draper and Stenbuck on the ulcer nose (straight, and lack of prominence, versus thin long in the male and short wide in the female).

I have tried to build up an approach to the explanation of the ulcer phenomenon by using known facts and a few assumptions. It seems worthwhile, from time to time, to stimulate oneself and others by looking at theories from the other side, and to take stock of facts which are not considered sufficiently by an important group of workers. While it was not possible to go into all arguments and to review all known facts, this presentation may stimulate further critical discussion and further investigative work.

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Hyperinsulinism - A Factor in the Neuroses

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A PATIENT ON WHOM A DIAGNOSIS of diabetes mellitus is made experiences a severe emotional shock. He realizes that he is confronted with a life of rigorous self-denial, punctuated daily stabs of the dreaded insulin syringe. One should expect diabetics to be highly "neurotic." However, the experience in practically all diabetes clinics reveals the astonishing fact that diabetics are, as a rule, very phlegmatic people. Indeed, it is usually the doctor who worries about their condition much more than do the patients. As a matter of fact, diabetics are notoriously poorly cooperative because they seem either unwilling or unable to treat their malady with its merited respect. Cajolery, explanation and even stern warnings and threats seem inadequate to break down the cavalier attitude most diabetics take toward their illness. One of us (E. M. A.) has been connected with diabetes clinics for the past twenty years and he has been repeatedly struck with the futility of even attempting proper control of his patients, especially since diabetes is the disease par excellence where the patient's cooperation is of the utmost importance.

The other author (R. H. H.) has been practising psychiatry for more than thirty years and during that long period he has had very little occasion to treat diabetics. The marriage of these diverse experiences has had this study as its offspring.

Diabetics are singularly unaffected by many ailments. They have, for example, much less than their expected allotment of allergic disorders (1, 2, 3), peptic ulcer (4, 5) and rheumatic fever (6). In these latter conditions, it was found that hyperinsulinism, the physiologico-pathological opposite of diabetes was uniformly present (7, 8, 9, 10). It has been recognized that manifest hyperinsulinism can be accompanied by marked psychic phenomena — depressive states, anxiety and other symptoms which have been lumped together as "neuroses" (11, 12). Derick, in a masterly review states that "hypoglycemia as a disease entity should be kept in mind constantly by all physicians, particularly those doing neuropsychiatric work. When seen

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for the first time and in the absence of a good history, the attack (of hypoglycemia) may suggest some brain disease, such as infection, neoplasm, or vascular accident. Because of their paroxysmal nature, the attacks may suggest epilepsy, acute alcoholism, amnesia, or some functional disorder such as hysteria. It is for these reasons that patients with hypoglycemia frequently are referred to neurological or psychiatric clinics." (13).

With these considerations in mind we have investigated 220 "neurotic" patients in whom the primary complaint was a mental depression or an anxiety state, revealing itself in the myriad and bizarre fantasies of the neurotic nature and disposition — phobias, suspicions, delusions, suicidal persuasions, etc. In some of our early cases, seen during 1946, the psychic disturbance was overlaid with an embroidery of physical symptoms which led us to suspect that they might have had hyperinsulinism accompanying their psychic disturbances. Since it has always been our procedure to submit psychiatric patients to thorough physical and laboratory investigation in order to uncover, and where possible to correct, any somatic disease, we included the six hour glucose test to determine the validity of this inference (11). Experience had taught us that the purely psychiatric treatment of many patients presented a far less intricate approach if the concomitant somatic factors were eliminated. We now found that many of these cases were victims of hyperinsulinism and treatment for that metabolic disturbance was instituted. We also found that the patients not only improved in their physical complaints but that their psychic symptoms waned and abated and that we had achieved an open sesame to those hidden and so-called subconscious conflicts that had hitherto presented adamantine resistance to psychiatric approach.

Our next step was to see whether subclinical hyperinsulinism might not be a background to the portrait of the neurotic, that is cases who made no reference to the classical symptoms of manifest hyperinsulinism such as hunger, sudden fatigue, etc. Our expectations in this regard were fulfilled in great measure. Many such patients did have hyperinsulinism and the correction of this purely metoblic disturbanct alleviated most of the anxiety symptoms. In other words, the psychic and somatic disturbances were treble and bass of the same discord.

The routine adopted was as herein outlined. After a preliminary history and complete physical examination, the patients were subjected to laboratory investigations consisting of the determinations of the basal metabolic rate, serum cholesterol, serum calcium and the six-hour glucose tolerance test. It has been our experience that hyperinsulinism is very frequently accompanied by hypocalcemia. This is supported by the work of Fabrycant and Pacella (14). Where indicated, other laboratory procedures, such as hematological studies, nitrogen determinations to indicate the hemopoietic or renal status, etc., were included. Since all of our patients were ambulatory and most had been fairly well worked up by their referring physicians, these additional procedures were only very rarely necessary.

The glucose tolerance test was devised by Seale Harris to reveal the presence of hyperinsulinism (11). In it, a fasting blood sugar level is determined and then the patient drinks a solution containing 100 grams of glucose. The blood glucose is then determined at hourly intervals for six hours. If the results are plotted, we get a curve like that shown (Fig. 1).

The diagnosis of hyperinsulinism is indicated by a significant drop below the normal level, say to 70 mgs. per 100 cc. of blood. Since the standard glucose tolerance test is so time-consuming to the patient and laboratory, we have modified it. A sample of blood was drawn after the B. M. R. was determined. This was used to obtain the blood glucose and serum calcium and cholesterol. It has been our custom to use the cholesterol level as a check on the accuracy of the B. M. R. Then the patient was given a bottle containing 200 cc. of 50% glucose solution or a proportionately smaller amount if his weight was significantly below 150 pounds. This was only rarely necessary. He was instructel to eat nothing after

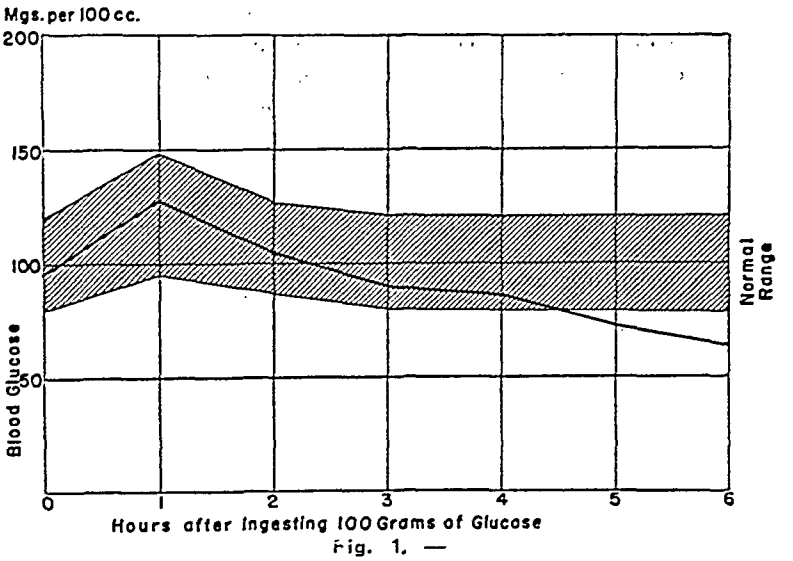


Fig. 1. —

The patients followed this diet religiously for four to six weeks. Harris has shown that there is one physical sign in hyperinsulinism, namely, left upper quadrant tenderness (11). Although it is very slight, we were able to elicit it in practically all of our patients. This tender area is symmetrically placed with respect to the point of tenderness in gall bladder disease. It probably overlies the tail of the pancreas. We also schooled ourselves to detect a slight spasm of the left rectus which was usually absent in its fellow. Concomitantly with the patient's subjective improvement, the tenderness and spasm diminished. When these objective findings had all but disappeared, the diet was modified to the following:

Breakfast — Fruit; cereal (dry or cooked) with cream or milk; one or two eggs with or without two slices of ham or bacon; only one slice of bread or toast with plenty of butter; beverage.

Lunch — Meat, fish, cheese or eggs; salad; vegetables; only one slice of bread or toast with plenty of butter; dessert; beverage.

Mid-afternoon — Glass of milk.

Dinner — Soup, if desired (not thickened with flour); vegetables; liberal portion of meat, fish or poultry; only one slice of bread, if desired; dessert (at this time, only, a sweet dessert may be taken); beverage.

Before Bed — Crackers and cheese; glass of milk. Any vegetable or fruit is permissable.

Beverages — Weak tea (tea ball, not brewed; Postum; Sanka Coffee; Kaffee Haag. May be sweetened with saccharine.

Desserts — Fruit; D-Zerta or other unsweetened gelatine; Junket (made from tablets).

Alcoholic and Soft Drinks — Club Soda; *dry* ginger ale; Whiskeys. Lettuce, mushrooms and nuts may be taken as freely as desired.

Take Only With Dinner — Potatoes, rice, cake, pie, pastries, custards, puddings and ice cream.

Avoid Absolutely — Sugar, candy and other sweets; Caffeine — ordinary coffee, strong brewed tea and "cola" beverages. Wines, cordials, cocktails, beer.

If you feel any sudden weakness, drink a small glass of fruit juice or milk.

We had thus eliminated most of the feedings between meals and had begun to permit more liberal carbohydrate consumption. The calcium injections discontinued.

In our early cases we repeated the glucose tolerance test and calcium determination before permitting any modification of the basic diet. We decided to eliminate this procedure and rely on our clinical impression because the patients were unhappily affected by the glucose tolerance test. The sudden loading of the circulation with the large unaccustomed amount of glucose upset the apple cart and the patients suffered a recurrence of their original complaints in varying degree and duration. From past experience, we had learned that bi-weekly injections of our calcium preparation for about a month were invariably sufficient to maintain a normal calcium level.

After another month or so, depending on the patient's response, we eliminated all dietary restrictions except moderation in the use of sweets and strict avoidance of caffeine. The patients were advised to make certain that they never went to bed hungry. Their bedtime snacks were entirely of their own choosing. In a few patients there still was an occasional wave of fatigue and depression which they soon learned to recognize before it became severe and they successfully combatted it by drinking an extra glass of milk or eating some fruit.

Instead of loading this report with a mass of unintelligible statistics, we will confine the clinical aspect to a brief discussion of the highlights of a few illustrative cases. The somatic treatment outlined above was interspersed with frequent psychiatric interviews. After as short a period as a week we noticed that our task in this regard became much easier and this improvement was progressive.

In each case, the laboratory findings will be recorded in this order — Basal Metabolic Rate (BMR), Serum Cholesterol (Chol), Serum Calcium (Ca) Fasting Blood Sugar (S-O), Blood Sugar fifth and sixth hours after ingesting 100 grams of glucose (S-5 and S-6) respectively.

Case 1. T. K. male, 43 years old. Had violent temper tantrums, usually at meal times, for six years.

Findings: BMR — Minus 3%; Chol — 212; Ca — 7.9; S-o-86; S-5 — 100; S-6 — 68.

After two weeks, the tantrums ceased completely and have not returned in sixteen months.

Case 2. B. L. female, 47 years old. Had claustrophobia for twenty years. Never left home unaccompanied. Never entered vehicle or elevator. Deserted by husband who couldn't put up with her fears and doubts.

Findings: BMR — Minus 6%; Chol. — 226; Ca — 8.6; S-0 — 85; S-1 — 175; S-2 — 121; S-3 — 104. S-4 — 100; S-5 — 103; S-6 — 66.

At the sixth hour she had palpitation, pallor perspiration. In three weeks, she entered subway, first with a companion, then alone. After two months, she took a trip of considerable distance, alone. Since then she has gone away for weekends, has gone to the theatre, and has run a self-service elevator. She has gained twenty lbs. and has lost all the vagotonic symptoms.

Case 3. S. I. female, twenty-one years old. Shy, diffident, introverted. Her mother was ill and the patient became despondent because of obsession that her mother had cancer. She anticipated her mother's death, and her own suicide. She had apprehensive nightmares, awakening from sleep in cold sweat. She came with a diagnosis of low blood pressure, anemia and tissue starvation. She had been treated with injections of vitamins and liver extract. She was resistive to all logical precept and example.

Findings: BMR — Minus 3%; Chol — 240; Ca — 9.3; S-0 — 79; S-5 — 73; S-6 — 62.

In one week she felt better. In a month she made a complete psychic adjustment to normal aspects of living and has been well for two years.

Case 4. H. S. male, sixty-four years old. Had been a successful executive and gave up business. He expatiated on shortcomings of life interminably. Was depressed, melancholy. Shock treatment had been advised.

Findings: BMR — Plus/minus 0%; Chol — 220; Ca 9.0; S-0 — 106; S-6 — 65.

In a month, there was a clearance of his depression and he resumed interest in working. Has become the treasurer of a large business enterprise and carries his duties without difficulty.

Case 5. J. P. male, thirty-eight years old. War phobic and apprehensive. Both parents had died of cancer and the patient neglected his large business for work with the cancer fund. He became gloomy, depressed and antisocial. Suffered chronic fatigue, headaches and vague abdominal distress. Gave up his activity in business.

Findings: BMR — minus 8%; Chol — 264; Ca — 8.5; S-0 — 84; S-1 — 146; S-2 — 126; S-3 — 96; S-4 — 82; S-5 — 78; S-6 — 61.

After two months he returned to his business with renewed interest and ambition. Stopped preoccupation with cancer. Has occasional wave of fatigue which invariably follows a few days excessive indulgence in sweets which he has now learned to eschew and he has had no complaints for eight months.

Case 6. A. B. female, fifty years old. Has had bouts of paroxysmal tachycardia accompanied by phobias and "cardiac neurosis" for many years. Was obsessive, a shut-in, rejected many offers of marriage. Went from one doctor to another — always in panic. Had claustrophobia and was afraid to go above third floor.

Findings: BMR — minus 7%; Chol — 215; Ca — 8.5; S-0 — 80; S-5 — 79; S-6 — 61.

At sixth hour, had severe tachycardia and was in panic. This was relieved by eating. After six weeks, her tachycardia disappeared. Has made normal adjustments, travels, works, has entered into active social life and now (one year later) has even climbed mountains and is now contemplating marriage!

Case 7. F. G. male, twenty-seven years old. Worked in literary field. Found that he could not write for lack of ideas. Became fatigued. Had recently married and increased responsibilities added to his worries. Had feeling of inadequacy. Felt drowsy after dinner.

Findings: BMR — plus 4%; Chol — 227; Ca — 9.2; S-0 — 86; S-5 — 86; S-6 — 67.

In less than a week he took a livelier interest in life and found that ideas came to him without effort. In addition to his employment as advertising copywriter he could take courses in evenings and is now writing "The Great American Novel."

Case 8. E. W. female, fifty-four years old. Hypersensitive for many years. Had a bilateral sympathectomy. Violent menopause. For seventeen years has gone out socially only four times! Has been treated by some fifty physicians and in twenty sanatoria. Shock treatment had been advised and she went to a sanatorium for that therapy but the attending physician there wisely disuaded her from it.

Findings: BMR: — plus 4%; Chol — 270; Ca — 8.9; S-0 — 144; S-1 — 160; S-2 — 120; S-3 — 66. Intense hunger. Palpitation, cold sweat at the sixth hour. Four days after treatment was instituted she asked her husband to take her to the movies! Has felt well, except for occasional menopausal flushes and hypertensive headaches, for over two years.

Case 9. M. M. male, forty years old. Recurrent periods of disinterested depression causing him to give up his business and to depend on family charity. Falls asleep right after each meal and while working.

Findings: BMR: — plus 18%; Chol — 170; Ca — 9.4; S-0 — 82; S-6 — 63.

After three months, he began to work managing a garage. Two years later repeat glucose tolerance S-0 — 84; S-6 — 78. Felt weak and phobic for about a week but that wore off and he is now (after another year) able to run his business.

Case 10. A. D. female, thirty four years old. Depressive with hysterical overtones, the latter usually in the morning.

Findings: BMR — minus 2%; Chol — [illegible]; Ca — [illegible]; S-0 — 87; S-5 — 74; S-6 — 62.

After six weeks was able to get along with the family and has continued to be well adjusted for almost two years.

Case 11. M. L. female, thirty one years old. Depressive, indifferent to great social opportunities.

Findings: BMR — minus 6%; Chol — 212; Ca — [illegible]; S-0 — 82; S-5 — 82; S-6 — 64.

In six weeks, weight rose from 94 to 102 Lbs. Began to take interest in family and society and has been well adjusted for eighteen months.

Case 12. A. B. male forty-three years old. Depressed. Claustrophobia (could not work because he could not ride in subway had what he called "stomach nervousness").

Findings: BMR — plus 5%; Chol — 219; Ca — 11; S-0 — 76; S-5 — 75; S-6 — 62.

The patient happened to have but one psychiatric interview (on his first visit). In five weeks he reported that he started to work going to his employment by subway.

Case 13. S. M. male, twenty-nine years old. Repeated neuroses of depression.

Findings: BMR — minus 8%; Chol — 245; Ca — 10.6; S-0 — 86; S-1 — 143; S-2 — 126; S-3 — 121; S-4 — 82; S-5 — 85; S-6 — 84.

This patient did not have hyperinsulinism but was given the diet. The psychiatrist of our team (BHH) who was unaware of this deception could get nowhere with the patient whose trouble was found to be largely depression due to financial stringencies which he was incapable of correcting.

Discussion

It has been our experience that the so-called neurotic — the individual who finds it difficult to accommodate himself comfortably to his environment — is so engrossed with his own misgivings that he is difficult to question and impress. Like light-struck plates his brain cells take dim and foggy pictures of suggestions made to him. He is negativistic, and self-interpretive. He listens more to the next question he is going to ask, or to the next compliant he is going to make, than to the most sincere adjurations of the psychiatrist. His brain is tired and ill-nourished. His fatigue has begotten apprehension and his apprehension has given birth to distortion-with all he whimpers many somatic complaints.

In the course of our discovery of a subjacent hyperinsulinism, together with a calcium deficiency and all that it implies in sympathetic imbalance, we found that the patients improved sufficiently during restoration of chemical and metabolic integrity to become much more receptive and responsive to psychiatric persuasion. It was then that we could show them where the shoe pinched, where the square peg was jammed into the round hole, where, in short, they were in conflict with the many aspects of life, and we were more than gratified to see these patients return to contented and profitable pursuits.

We like to explain this amazing change in behavior by saying that our patients had had hunger not only

of the body but of the mind as well and when their brains were bathed with a nutrient fluid richer in sugar they "accepted the rewards and buffets of life with equal thanks." In fact, Fabrycant and Pacella (14) have also shown electroencephalographic changes in hyperinsulinism. And a report recently published indicates that "mental patients do not mobilize the sugar in their body in response to mental stress" (19). Our explanation for this finding lies in the antagonistic actions of adrenalin and insulin — the surfeit of the latter nullifies the effect of the former.

NOTES

Case No. 1. Shows the relationship between hypoglycemia and the emotions. The tension came on at meal time when the blood sugar is low and a more tranquil behavior followed the post post-prandial rise in blood sugar.

Case No. 3. The nocturnal symptoms came at times when hypoglycemia is most apt to occur.

Case No. 5. This patient demonstrates the necessity for eternal dietary vigilance as the price of psychic peace.

Case No. 7. This patient had excessive appetite. Had been voraciously hungry at dinner time and had to dine before his wife reached home (a little later than he did).

Case No. 9. The fatigue came on before meals and he noticed he was more alert about a half hour after eating.

Case No. 10. The hysterical outbursts occurred on arising — again during the hypoglycemic period.

Case No. 12. This patient was his own psychiatrist. He found that he became indifferent to trivial matters which had angered him. The "stomach uneasiness" has been shown to be a possible effect of hyperinsulinism (20).

Case No. 13. This patient had a personality and intellectual inadequacy which, of course, was entirely unaffected by any diet. He is included to show, by contrast, how those cases in which a correctable hypoglycemia exists became more amenable to suggestion as the nutrition of the brain improves. In this case the trouble was not nutrition but in the capability of the organ itself.

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Methionine

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I Discovery

In 1922, MUELLER (1 to 5) announced the discovery of a sulfur-containing amino acid in casein hydrolysates to which he finally gave the empirical formula $C_5H_{11}SNO_2$. Curiously enough this was brought about through microbiological research relative to the growth of the streptococcus. When eventually this amino acid was isolated in a pure form, it showed no particular influence on the growth of the microorganism.

Mueller's procedure for isolation of this amino acid may be summarized as follows: The acid hydrolysate of casein was treated with mercuric sulfate at a neutral reaction to litmus. The precipitate was washed and extracted four times by two per cent hot barium hydroxide. The extracts were freed from mercury and then from barium. After concentrating the filtrates, mercuric chloride was added and the precipitate formed was washed and treated with barium sulfide. Reagents were removed and the filtrate was next concentrated *in vacuo*. A crystalline product was obtained which was subjected to further purification and recrystallization. The final yield varied from 0.2 to 0.4 per cent of casein.

In 1925 Odake (6) investigated yeast extracts and succeeded in isolating a crystalline substance possessing the properties of Mueller's amino acid. Barger and Coyne (7) were first to synthesize this amino acid, and after consultation with Mueller, suggested the name METHIONINE in allusion to its structural formula:

$$CH_3\ S\ CH_2\ CH_2\ CH(NH_2)\ COOH$$

Gamma-Methylthiol-alpha-aminobutyric acid

The isolation of methionine was also investigated by Pirie (8) and by du Vigneaud and Meyer (9). Biochemical methods for the isolation of this amino acid in a pure state gave very low yields which for more than two decades accounted for the high cost of this product.

II Synthesis

DL-methionine has been synthesized by numerous investigators with varying yields.

Barger and Coyne's (1) attempt to synthesize this amino acid by the hydantoin method was not successful. They accomplished its synthesis by first preparing beta-methylthiolpropionaldehyde and subjecting the resulting product to the modified Strecker's reaction. The over-all yield was only 3.4 per cent of the theoretical amount. Windus and Marvel (2) employed a malonic ester synthesis and their method was modified by Emerson, Kirk and Schmidt (3) with slight improvement in yield. Barger and Weichselbaum (4) applied the phthalimidomalonic ester synthesis and shortly after that Hill and Robson (5) reported another synthesis. Graham and Schweitzer (6) re-investigated Barger and Coyne's original method and effected some improvement in yield. Lacky (7, 8) studied the acid hydrolysis of methionine-nitrile and claimed substantial gain in yield, mostly by refinement in technic.

The synthesis of DL-methionine containing excess quantities of the stable isotopes S^{34} and C^{13} in the beta and gamma positions was accomplished by Kilmer and du Vigneaud (9). Melville, Rachelle and Keller 10) reported the synthesis of L-methionine containing C^{14} in the methyl group. Livak, Britton, Vander Weele and Murray (11) obtained DL-methionine by the alkaline hydrolysis of 5-(beta-methylmercaptoethyl)-hydantoin.

III Determination of Methionine

Methionine may be determined by (1) chemical and (2) microbiological methods. The latter methods account for only 50 per cent of DL-methionine.

(1) *Chemical Methods:* By virtue of the labile methyl group in methionine, Barger and Coyne (1) pointed out that this amino acid may be determined by demethylation with hydriodic acid and the resulting methyl iodide may be quantitatively estimated. Baernstein (2) applied this principle for the determination of methionine found in proteins. His procedure became known as the "methyl iodide method;" however on further investigations, numerous workers found that it gave high values for this amino acid. Bailey (3), Kassel and Brand (4) Kuhn, Birkofer and Quackenbush (5) and Lavine (6) suggested several refinements and modifications for Baernstein's method. Beach and Teague (8) reported a gravimetric method.

McCarthy and Sullivan (9) found that methionine forms a colored compound with sodium nitroprusside. They developed a satisfactory, and rapid colorimetric method which is now widely used. White and Koch (10) offered minor modifications. Tutiya (11) proposed a colorimetric method based on fusion of methionine with sodium hydroxide, aeration of the solution into isatin and measurement of the green colored compound developed.

(2) *Microbiological Methods:* Assay of amino acids by microbiological methods involves the use of certain groups of bacteria known as *test organisms*. These may be divided into two groups: (a) *Homofermentative*, which comprises bacteria that are capable of almost quantitatively converting glucose to

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lactic acid and (b) *Heterofermentative*, which can convert glucose into lactic acid and other degredation proucts such as ethyl alcohol, acetic acid, carbon dioxide, etc.

Although many organisms have been employed for microbiological assay of amino acids, only a limited number have been carefully studied and recommended by workers in this field. One reason is that different strains of the same species may not give the same response or may differ from one another as to their specific nutritional requirements.

Several microbiological methods for the estimation of methionine have been developed. References to these methods and to the *test organisms* employed are:

Test Organisms	*References to Microbiological Methods for Estimation of Methionine*
Streptococcus faecalis	14, 15, 19, 20, 21, 22, 23, 24
Leuconostoc mesentroides	16, 18, 19, 20, 21, 22, 23, 26, 27
L. Arabinosus	17, 20, 23, 24, 26, 28
L. Casei	20
L. Fermenti	20, 26, 29
L. Delbruckii	20

Measurement of Results: The results may be obtained either by turbidimetric or titrimetric measurements.

For turbidimetric measurements of bacterial growth, photoelectric colorimeters are generally used. Readings are recorded, plotted and checked against a standard reference curve that had been constructed, or as galvanometer readings against the known amount of the standard amino acid used. For titrimetric measurements, the acidity of a sample is determined by titration with a standard alkali. For details on criteria for accuracy see Snell (30, 31).

IV Metabolism of Methionine

For many years prior to the discovery of methionine, cystine was the only component of proteins known to contain sulfur. The first cystine was investigated by Osborne and Mendel who observed, that when 18 per cent of casein was incorporated in anotherwise adequate diet young rats receiving such a food mixture grew at normal rates. However, when proportions of casein was progressively decreased in the diet, the rate of increase in body weight was inhibited (1). The percentage of cystine in casein was known to be very small and consequently it was assumed that this amino acid was the limiting factor. On the basis of these findings cystine was considered an essential amino acid. Several investigators confirmed these observations and not until Jackson and Block (2) reported the addition of methionine to a diet low in casein promoted growth in the rat, that the indispensable nature of cystine was doubted. The findings of Jackson and Block were confirmed by Weichselbaum et al. (3). Even then, the dispensability of cystine and the indispensability of methionine were not as yet fully established.

(1) *Indispensability:* Since experimental evidence based on diets of protein mixtures is not conclusive to demonstrate the indispensable nature of an amino acid, pure amino acids must be utilized for such purposes. To insure the exclusion of cystine and methionine from a ration, each amino acid employed in the preparation of a mixture of amino acids must be of the utmost purity and free from contamination of other amino acids. Rose and his associates (1) were first to employ such a procedure and painstakingly prepared and recrystallized each amino acid in the diet they used. The cystine employed as a supplement was recrystallized six times until correct chemical data had been obtained. The methionine investigated was a recrystallized synthetic product. Rose's elaborate experiments showed that the addition of cystine to a diet deficient in methionine and cystine was practically without any effect and the animals lost weight; on the other hand the incorporation of methionine in such a diet permitted rapid growth. Thus, his data provided the first convincing proof of the dispensability of cystine and the indispensability of methionine. Beach and White (4) also reported that methionine stimulated the growth of animals previously stunted by a diet in which arachin served as the protein; whereas cystine under the same conditions yielded no growth-promoting effect.

The demand for methionine by different animal species and by man is indeed of major importance in nutrition; for the content of sulfur is large in keratin proteins such as wool, hair, nails, hoofs, etc., in hormones such as insulin and in many organs of the animal system. Thus adequate quantities of this amino acid must be present in food-intake to satisfy body requirements. There is considerable evidence in the literature that many well known foods for human and animal consumption are so limited by their methionine and cystine content that the index of their biological value is indeed low. By incorporating methionine in such foods an enchancement of their utilization ensues, hence a decrease in the amounts of food intake. The following foods and proteins given in Table I are low in methionine or methionine and cystine.

TABLE 1*

Percentage Deficiency in Cystine and Methionine as Compared with the Proteins of whole Egg. The Data Reported are Based on Chemical Analysis and on Estimation of Biological Values.

Food Protein	Limiting Amino Acid	Deficiency Per Cent	Methods Chemical	Methods Biological
Beef muscle	Cystine and Methionine	29	C	B
Horse muscle	Cystine and Methionine	35	C	—
Chicken muscle	Cystine and Methionine	31	C	—
Crustacean muscle	Cystine and Methionine	25	C	—
Kidney	Cystine and Methionine	35	C	—
Blood-globulins	Cystine and Methionine	73	C	—
Cow's milk	Cystine and Methionine	32	C	B
Casein	Cystine and Methionine	42	C	B
Human milk	Cystine and Methionine	46	C	B
Human colostrum	Cystine and Methionine	34	C	—
Corn germ	Cystine and Methionine	61	C	—
Navy bean	Cystine and Methionine		—	B
Phaseolin	Cystine and Methionine		—	B
Lima bean	Cystine and Methionine		—	B
Adzuki bean	Cystine and Methionine		—	B
Soybeans	Cystine and Methionine	10	—	B
Peanut	Cystine and Methionine	76	C	—
Arachin	Cystine and Methionine	83	C	B
Pea, field	Cystine and Methionine	66	—	B
Pea, garden	Cystine and Methionine	66	—	B
Alfalfa	Cystine and Methionine	40	—	B
Leafy vegetables	Cystine and Methionine	44	C	—
Yeast, brewers'	Cystine and Methionine	55	C	B

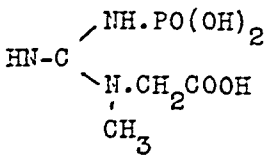
*This table is abstracted from Mitchell's chapter II, M. Sahyun, Proteins and Amino Acids in Nutrition, Reinhold Pub. Corp. N. Y. 1948.

2 *Mechanism of Conversion of Methionine to Cystine:* Throughout most of the literature bearing on phases of metabolism of these two amino acids, the mechanism of conversion *in vivo* of methionine to cystine has been subject of considerable research. In the absence of inadequate supply of cystine in the diet, methionine is converted, probably in the liver, to cystine, but the reverse is not true. The details of the chemical reactions involved are not fully established. With the advent of radioactive elements such as S^{35}, C^{13}, C^{14} and deuterium, different preparations of DL-methionine containing one or more of these elements in various positions in the molecule were synthesized and fed to experimental animals. Tarver and Schmidt (5) showed that the radioactive sulfur of methionine they synthesized is transferable to cystine in the animal body. They also reported that methionine can fulfill all the functions of cystine. Stekol (6) observed that there was no immediate elimination of sulfur nor of nitrogen when either cystine or methionine was given to rats receiving a low protein diet. This investigator concluded that since there was no diminution in the excretion of nitrogen derived from the protein of the diet and from endogenous sources, the retained cystine and methionine were not used to form protein but stored in some other form. Madden and his coworkers (7) observed negative nitrogen balance to take place in the experimental dog when cystine and not methionine was the source of amino acid sulfur in the diet. Of considerable importance is the recent findings of du Vigneaud et al. (8) who synthesized methionine with isotopes of sulfur and carbon in the *beta* and *gamma* position respectively and fed it to rats. They reported: "On isotopic analysis of the cystine that approximately 80 per cent of its sulfur but no significant amount of its carbon had been derived from the tagged methionine." Thus there has been secured conclusive experimental evidence which establishes that the carbon chain of methionine is not utilized in *in vivo* conversion of methionine to cystine. Since the sulfur of methionine has been found to be transferable to cystine, it has been suggested that the remainder of the molecule could be derived from that of serine.

3 *Relation of Methionine to Creatine:* The origin of creatine in the animal system, its relation to amino acids, to creatinine and its metabolism have long been subjects of considerable interest and debate. One reason for the unusual interest in this compound has been the startling revelations made less than two decades ago by Lundsgaard on the mechanism of muscular contraction. Previously, it was assumed by physiologists that the energy released from the breakdown of glycogen to lactic acid was responsible for muscular activity and that muscle fatigue was caused by the accumulation of lactic acid *in situ;* also that muscular contraction was not resumed until the lactic acid formed was converted to glycogen, one fifth of it being oxidized to carbon dioxide and water and the remaining four fifths being used for glycogen synthesis. Lundsgaard demonstrated that the poisoning of muscle with monoiodoacetic acid would permit muscular contraction even though lactic acid was

not produced. This meant that the process of contraction and the production of lactic acid were not inseparably connected. Subsequently, it was discovered that the process of muscular activity was the result of the tremendous energy released by the breakdown of a substance known as phosphocreatine the chemical structure of which is:

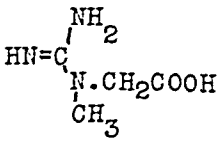
Phosphocreatine



Phosphocreatine was isolated from the extracts of skeletal muscle by Fiske and Subbarow in 1927 and they together with the Egglestons proved that during muscular contraction, this compound was hydrolyzed to phosphates and creatine, and was resynthesized during the period of muscular recovery. When a muscle is poisoned with monoiodoacetic acid it contracts as long as there is phosphocreatine available, but unlike normal muscle, resynthesis of phosphocreatine does not take place, hence contraction ceases.

Obviously Lundsgaard's discovery and the findings of Fiske and Subbarow and of the Egglestons, aroused considerable interest in the origin of creatine in the system. Creatine has the following chemical structure:

Creatine



Herein, we are only concerned with the relationship that exists between creatine and methionine.

As can be seen from the above configuration of creatine the presence of a methyl group is indeed important. Apparently the animal system is unable to synthesize labile CH_3 and for the *in vivo* synthesis of compounds containing it, the methyl group must be borrowed (or preferably transmethylated) from other compounds that have the ability to lend it or donate it.

Borsook and Dubnoff (9) reported that liver slices synthesized creatine from guanidoacetic acid *in vitro* and that this reaction was accelerated by the addition of methionine. Their findings were confirmed by Bodansky, Duff and McKinney (10). The amidine group of creatine was also shown to originate from arginine by Block and Schoenheimer (11) by means of their isotope experiments. However, it remained for du Vigneaud and his associates (12, 13) to prove by means of isotopic elements in DL-methionine, that this amino acid contributed its methyl group for the completion of the synthesis of creatine.

4 *Ultimate fate of Methionine in the system:* Since it has been definitely established that methionine is the precursor of cystine in the animal body and the latter has numerous metabolic functions and gives rise to a variety of sulfur-containing compounds, therefore methionine assumes all the prerogatives of cystine. Hitherto, no different channel is known than that of cystine that explains the ultimate oxidation of this sulfur-containing amino acid. Lewis (14) has shown that methionine is oxidized more slowly than cystine in the normal course of metabolism. The simultaneous oral or parenteral adminstration of these two substances revealed that methionine remained longer in circulation and formed sulfate more slowly than cystine did. This indicates that the first step of methionine breakdown is its conversion to cystine. The latter is next reduced to cysteine. Medes (15) extracted from livers of animals enzymes which oxidized the sulfur of both cystine and cysteine to sulfinic acid and the latter was eventually converted to sulfate.

Smuts, Mitchell and Hamilton (16) demonstrated that a diet deficient in this sulfur-containing amino acid inhibited the growth of rats and their hair. Payne and Perlzweig (17) observed that the fingernails of pellagrous patients (due to nicotinic acid deficiency) were low in cystine. Sullivan and Hess (18) reported similar findings in chronic deforming arthritis. Peters (19) reported improvements in two cases of dermatitis following the administration of cystine. An analysis of the "scaly skin" of these patients showed that one-third of the dietary cystine was lost in the exfoliation.

Insofar as has been presented no mention has been made of the fate of the labile methyl group of methionine. As we shall see later, this important group in methionine has considerable significance in metabolism of fat. Recently, MacKenzie and his associates (20) fed methionine-containing isotope C^{14} in the methyl radical to rats and reported the presence of radioactivity in the carbon dioxide collected even at the end of only one hour. This is a conclusive evidence that the labile methyl group when ingested as methionine can be oxidized to carbon dioxide.

5 *Detoxication Mechanism:* It has been observed (21) that when a toxic substance like bromobenzene is fed continuously to rats, a deficiency in the sulfur-containing amino acids occurs. This deficiency is accomplished by retardation of growth and loss of weight and can be corrected by the intake of adequate amounts methionine, cystine and homocystine (22). Cessation of growth and loss of weight following bromobenzene poisoning are explained on basis of utilization of these amino acids for conjugation mechanisms and the *in vivo* synthesis of mercapturic acids; thus preventing methionine from the pursuit of its normal metabolic functions. A similar deficiency has also been noted in animals fed biphenyl or chrysene and this toxicity was shown to be alleviated by methionine, cysteine and glutathione (23, 24, 25).

The administration of one per cent nicotinic acid

or its amide to rats causes toxic manifestations with concomitant loss of weight. Nicotinic acid apparently creates a labile methyl group deficiency which has been shown to be counteractable by methionine alone and not by choline, cystine or homocystine alone. Choline can be rendered effective against nicotinic acid poisoning if given in conjunction with cystine or preferably homocystine (26, 27).

High protein diets have been known to exert a protective mechanism in animals exposed to the toxic effects of selenium, trinitrotoluene, arsphenamine and mapharsen. The effective agent in proteins against these poisons was recently found to be methionine (28, to 37). In the depleted dog, Miller et al. (38) found that methionine and to a lesser extent cystine protected the animal against the ill effects of chloroform.

Baxter (39, 40) investigated the toxicity in rats of 0.1 to 0.2 per cent pyridine hydrochloride added to a diet moderately low in protein (10 per cent casein) and noted cessation of growth and eventual death within two weeks in most of the experimental animals. The supplementation of the diet with 0.5 per cent methionine permitted growth and increased to a limited extent the survival time. Baxter and Mason (41) studied the relationships between the mechanisms of the liver and kidneys injury produced by pyridine and other similar toxic substances and mechanisms of diets deficient in choline and methionine. They found that in contrast with the beneficial influence of methionine the addition of choline to a diet moderately low in protein and containing pyridine afforded no protection to the animal. They therefore concluded that pyridine causes a drainage on the labile methyl group of methionine but not of choline.

In his recent discussion "Conditioning Factors in Nutritional Disease" Ershoff (42) states. "On a low protein diet, insufficient amounts of such amino acids may be present to meet the requirements for maintenance plus detoxification with the result that an amino acid deficiency may develop. The effects of such a deficiency will be particularly marked in the liver cell, since the liver is the organ where detoxification primarily occurs. The hepatotoxic effects of chloroform, carbon tetrachloride and other toxic substances may be explained therefore, at least in part, on the basis of methionine deficiency in the liver cell. Particularly pertinent in this regard is the similarity of symptoms resulting from a dietary deficiency of methionine with that obtained on the administration of noxious substances requiring methionine for detoxification. It appears further that the body will employ nutrients preferentially for detoxification, even at the expense of sacrificing its own tissues to obtain the required material."

Bearing in mind that methionine in the animal system assumes all the prerogatives of cystine, the available information on the subject of detoxication indicates that its requirement must be sufficiently met to insure adequate supplies in the body of this amino acid for: (1) labile methyl group, (2) conjugation mechanism, (3) synthesis of mercapturic acids, (4) fatty liver infiltration, (5) normal metabolic functions and (6) maintenance of positive nitrogen balance and (7) growth.

6 Methionine Deficiency: The complete absence of methionine from the diets of experimental animals causes cessation of growth, loss of hair and eventual death. Dietary relationships between methionine and cystine have already been discussed. It is now definitely established that cystine alone does not stimulate growth in the complete absence of methionine but it causes stimulation of growth in the presence of suboptimal amounts of its precursor (43). Appropriately, Rose stated:

"These facts serve to emphasize the importance of knowing the exact composition of the ration before drawing positive deductions from the growth behavior of the animals."

There is a paucity of literature dealing with pathological changes occurring in animals kept on diets deficient not only in methionine but in suboptimal amounts of this and other indispensable amino acids. Widespread famines in Europe, in Asia and shortages of proteins for foods and feeds should certainly cause a much greater stimulus for such studies than have hitherto been made. Unquestionably, it is not enough to know that a certain amino acid is important in our diet and whether or not it is indispensable to the experimental animal, but more so the consequences of deficiency, particularly when the diet contains sub-optimal quantities of any of the essential amino acids and of any pathological changes that may occur in the essential organs of the body.

Glynn, Himworth and Neuberger (44) kept rats on a diet deficient in methionine and cystine and observed the development of massive hepatic necrosis and excretion of homogentisic-like compounds. These abnormalities were noted to be preventable when either cystine or methionine was added to the deficient diet. Neuberger and Webster (45) as cited by Cutherbertson (46) reported that a deficiency of the sulfur-containing amino acids decreases the ability of the body to metabolize aromatic amino acids to such an extent that even with small intake of tyrosine and phenylalanine considerable amount of a homogentisic-like acid is excreted. Cystine alone partially protects the animal against this alcoptonuria They suggested that the important factor which is responsible for the development of necrosis, is the deficiency of cystine and that the protective effect of methionine is due to its being a precursor of cystine in the body.

Wanscher (47) found that rats kept on a five per cent casein diet develop: (1) severe degeneration of liver cells concomitant with hemmorhage and intestinal inflammation, (2) degeneration occurring in the convoluted tubules of the kidneys and (3) not infrequently severe chronic convulsions. Increasing the amount of casein in the diet from five per cent to 10 per cent gives no protection to these ani-

mals, but the addition of as little as 0.2 per cent of methionine restores normal growth and causes regeneration of hepatic tissue. The addition of cystine alone yields only partial protection, but does not prevent loss of weight, whereas cysteine affords no beneficial effect whatsoever. Sydenstricker et al. (48) observed corneal vascularization in rats kept on methionine deficient diets.

It has recently been reported that chloretone and phenobarbital accelerate the urinary excretion of vitamin C in the rat and cause increased concentration of this vitamin in the small intestine, kidneys, liver and to a lesser extent in the spleen (49). Roberts and Spiegel (50) pursued the latter investigation on rats kept on a five per cent casein diet and reported that ability of these animals to excrete ascorbic acid in response to either chloretone or phenobarbital is greatly limited, as compared with those kept on a diet of 18 per cent casein. The addition of methionine, cystine or both, to the five per cent casein diet, in amounts to bring up the sulfur content to that of the 18 per cent casein level, increase the excretion of vitamin C of rats treated with either chloretone or phenobarbital. They are, therefore, of the opinion that methionine and cystine do not act directly as precursors to vitamin C in the rat, but that the accelerating influence they exert on vitamin C excretion is related to the generally beneficial effect observed when they are added to a low protein diet.

5. Interrelationship of Methionine, Cystine and Choline in Fatty Livers

The exclusive accumulation of fats in the liver may either arise from exaggerated physiological circumstances or from pathological conditions. As a rule physiological and pathological fatty livers are distinguished, not only by the quantity of lipids they contain, but also by the character and partition of these lipids.

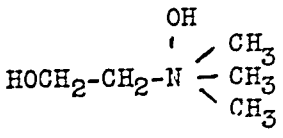
The excessive accumulation of fats in the liver has been recognized since 1889 when Minkowski performed his classical experiment of extirpation of the pancreas in dogs. The development of hyperglycemia and glycosuria in the depancreatized animal overshadowed that of fatty livers. Not until the discovery of insulin took place and the need felt for depancreatized animals to pursue furthur research on carbohydrate metabolism was it realized that insulin alone would not suffice to maintain life in the depancreatized animal. Following pancreatectomy, an impairment of liver function ensues with rapid accumulation of lipids and ketone bodies (1). Since the only difference between the depancreatized and the intact animal is the removal of the pancreas, it was found necessary to include raw pancreas in the diet of such animals to permit normal hepatic functions while insulin is being parenterally administered to control blood sugar. Hershey and Soskin (2) also discovered that egg-yolk-lecithin could replace raw pancreas in the diet of the depancreatized animal and restore normal liver function. Thus the term *Lipotropic* has been applied to such substances that are capable of eliminating excessive accumulation of fat in the liver caused by dietary deficiencies.

Individuals with pathological fatty livers do not consume an undue amount of fat in the diet nor is there an excess of lipids in the blood stream. In effect there is a diminution of blood lipids, a reduction in cholesterol esters, phosphatides and a disturbed pattern of hepatic lipids. These pathological disorders arising from dietary deficiencies will ultimately lead to a degeneration of liver cells and cirrhosis and not infrequently are accompanied by hemorrhages and degenerative lesions in the kidneys.

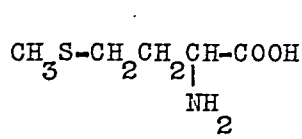
According to Peters and Van Slyke (3), "In almost every instance dietary fatty livers have been traced to the absence from the diet of some components essential for the synthesis of phospholipids or the presence of some compound which interferes with their synthesis."

Two of the important dietary factors that have been investigated and found to possess lipotropic activity are choline and methionine. Although these two compounds radically differ from one another in their chemical composition, as can be seen from their structural formulae, nevertheless they do possess one virtue in common, viz. *labile methyl group.*

Choline

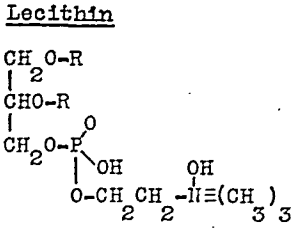


Methionine



It has been pointed out earlier in this discussion that lecithin (phosphatidyl choline) found in egg yolk was capable of preventing fatty infiltration in the liver of the depancreatized dog. The findings of Hershey and Soskin were subsequently confirmed by Best and his associates (4) who also demonstrated that the active liptropic agent in lecithin is choline. Further research in this field led to the observation that the livers of animals kept on choline-deficient diets, but containing adequate amounts of casein and sucrose, did not accumulate fat. An investigation of the active liptropic agent in casein soon revealed, that, whereas cystine added to diets deficient in choline and methionine caused fatty liver infiltration in the experimental animal, both *d* and *l* methionine did not.

Lecithin



The mechanism of action of choline and methionine in preventing fatty liver infiltration was undertaken and by preparation of compounds containing isotopes of H, C, and S the transmethylation theory was

evolved.

Transmethylation: In reviewing the subject of interrelationships between choline and other methylated compounds, du Vigneaud (5) stated, "The concept that methylation was a general metabolic process was, in fact, explicitly stated some fifty years ago by Hoffmeister (1894) who in his studies on the methylation of tellurium suggested the formation of choline and creatine might be due to the same methylating mechanism. He even postulated that for the purpose of methylation, a methyl group might be split off from some precursor and attached to the new moiety."

On demethylating methionine in the animal system, it has been shown that homocystine is the first intermediate product. Du Vigneaud, Chandler, Moyer and Keppel (6, 7) demonstrated that rats receiving homocystine in a diet deficient in both methionine and choline were unable to grow. However, it was found that homocystine could support growth of animals on a methionine-free diet only in the presence of choline or betaine. These observations were confirmed by others (8, 9). It therefore appears that choline had probably acted as a donor of a methyl group for the synthesis of methionine from homocystine.

The lipotropic action of methionine is apparently due to its ability to contribute methyl groups for the synthesis of choline from ethanolamine (10). Evidence for the latter compound as the source of nitrogen of choline is found in the experiments of Stetten (11) on rats in which the feeding of ethanolamine containing N^{15} led to the *in vivo* synthesis of choline containing labelled nitrogen.

Although both choline and methionine are considered excellent transmethylating agents in the animal system, their paths only cross at certain intersections in this complicated system of fat metabolism and evidently only in this respect do they perform similar functions. Thereafter each assumes more specific roles in metabolism. Choline, for example, is not entirely dependent on its labile methyl group for its liptropic activity whereas methionine performs this function only by donating its methyl group for the *in vivo* synthesis of choline. The latter is an essential precursor of lecithin and the exact mechanism of its lipotropic activity is yet to be elucidated.

The lipotropic activity of a large number of compounds has been investigated and only those substances which can form choline or donate their methyl groups for its synthesis were found physiologically active in preventing fatty liver infiltration. In the investigation of casein as a substitute to choline as a lipotropic agent, several workers (12, 13, 14) were unable to account for the total lipotropic activity of this protein by its methionine content. In view of this, a number of amino acids have been tested and found devoid of this activity. Some observers (14) implied that the opposing action of cystine and methionine together could explain the whole lipotropic effect of casein.

Several substances are known to produce fatty livers in the experimental animal despite the presence of protective doses of choline. Among these is guanidoacetic acid (15). This compound apparently exerts its effect by requisitioning the methyl group from choline or methionine for the synthesis of creatine. Like most agents that give rise to fatty livers, guanidoacetic acid induces characteristic lesions in the kidneys.

Ever since its discovery, cystine has ever been an elusive compound and some one hundred years were required to establish its exact chemical structure. Being a sulfur-containing amino acid it has occupied stellar roles in the metabolism of amino acids. As methionine replaced cystine in its classification among the indispensable amino acids, investigators in this field were again puzzled by the peculiarity of cystine to promote hepatic fat infiltration. In young rats, for example, 0.3 per cent of this compound did as much damage as 1.0 per cent and no greater quantity of choline was necessary to counteract the large dose than was needed for the small dose (16). This effect of cystine was considered by some workers to be connected with methylation. This explanation is also applicable to homocystine which also induces hepatic fat infiltration, and which has been shown by isotopic studies to be a methyl receptor.

The liver fattening effect of cystine, according to Griffith (16, 17) may be accounted for by the appetite-stimulating effect it produces, thus exacting a greater demand for chlorine or methionine in the diet. This obviously indicates that this particular effect of cystine is not due to any specific toxic action nor to a direct interference with the process of fat transportation. Griffith and Mulford (18) reported that the incidence of fatty livers in rats is related to food-intake. For the prevention of fatty livers caused by cystine, adequate amounts of either choline or methionine must be incorporated in the diet. Thus in rats on choline deficient diets and just enough methionine to prevent hepatic fatty liver infiltration, cystine enhances appetite and causes deposition of fat in the liver. This effect is greater in young growing rats than in mature animals (19, 20).

Recently, Stetten and Salcedo (21) showed that the administration of heavy water to rats kept on choline deficient diets resulted in the findings of deuterium only in the fatty acids of the liver, while the addition of cystine to the diets of animals similarly treated, their livers were equally fat however deuterium was found in the fatty acids of the liver and in the fatty acids of the carcass. It may therefore be concluded that cystine is a general fattening agent whereas the lack of choline seems to block the movement of fat from the liver to other tissues of the body.

VI METHIONINE IN NORMAL HUMANS AND IN HEPATIC CIRRHOSIS

This amino acid has been shown by numerous in-

vestigators (1 to 4) to be indispensable to man. Its quantitative requirement in the normal adult human has not as yet been fully established. According to Rose (5) the upper limit of man's daily intake of this amino acid is 50 mg. per kilogram of body weight or 3.50 gm. for a man weighing 70 kg. In deficiency disorders and in certain metabolic dysfunctions additional supplements of methionine are required.

In 1941, Gyorgy and Goldblatt (6) observed that necrosis or cirrhosis of the liver would develop in rats on a low protein-intake and that the administration of choline would prevent the development of these syndromes. Daft, Sebrell and Lillie (7) confirmed their work and added that some protection to the liver was afforded by the addition of choline and methionine or by methionine alone. In 1942, Fagin, and Zinn (9) and in 1943, Fagin, Sahyun and Pagel (10) clinically investigated the lipotropic activity of an amino acid mixture and reported that liver specimens from patients with cirrhosis of the liver due to chronic alcoholism, who had received amino acids, contained a greater percentage of protein and a lesser percentage of fat than specimens liver specimens from patients with cirrhosis of the from patients who had not received amino acid therapy. They postulated that the lipotropic activity of the preparation they used was primarily due to its methionine content. In 1944, Beattie and Marshall (11) published their observations on a case of a young soldier with infective hepatitis who fully recovered following the injection of methionine; however they stated that in chronic cases superimposed on a pre-existing cirrhosis there might be limited improvement with methionine therapy. Barclay et al. (12) intravenously administered 10 gm. of methionine daily and obtained dramatic results in two patients with infective hepatitis; they felt that the failure of Higgins et al (13) to achieve similar results was due to the inadequacy of the dosage the latter used in their clinical studies. Barclay and Cooke (14) also obtained excellent results when both choline and methionine were intravenously injected into a patient who had severe hepatorenal injury as a result of large doses of barbiturates. Wilson, Pollock and Harris (15) orally administered methionine to 52 patients with infective hepatitis and found a significant shortening of the period of recovery as compared with 51 control cases who had not received methionine. Ferriman, Williams and Cadman (16) gave methionine to a patient with subacute necrosis and two months after the methionine treatment reported complete recovery. Eddy (17, 18) studied the effect of this amino acid in patients with toxic hepatitis caused by trinitrotoluene and carbon tetrachloride poisoning and obtained favorable results. In 1947, Morrison (19) after a careful clinical study of methionine and choline therapy that extended over three years stated that patients treated with these agents showed greater improvement, a lower incidence of mortality and a more definite decrease in ascites than those patients managed without methionine and choline. The recent observations of Beams and Endicott (20) point decisively toward the effectiveness of methionine alone in the treatment of cirrhosis in the decompensated stage. They showed by means liver biopsies definite histologic changes and clinical improvement particularly in hepatic function (demonstrable by liver function tests). These investigators recommended an average daily dose of two to five gm. of DL-methionine as a dietary supplement for the treatment of cirrhosis of the liver.

SUMMARY

1. Methionine is an indispensable amino acid to the diets of man and animals. Cystine is not, but its inclusion in the diet enhances growth of animals and spares to a certain extent the demand on methionine by the body.

2. Methionine has been reported to play an important role in detoxication mechanisms to such poisons as chloroform, trinitrotoluene, nicotinic acid, selenium etc. and certain observers indicated that it could prevent liver injury due to barbiturate poisoning.

3. By virtue of its labile methyl group, methionine possesses lipotropic activity. This property is explained on its ability to donate its methyl group to the *in vivo* synthesis of choline.

4. By means of isotopic studies this sulfur-containing amino acid has been shown to be the precursor of creatine in the body, hence it is indirectly concerned with phospho-creatine and its relation to muscular activity.

5. For normal adult humans the upper limit of methionine requirement is 50 mg. per kg. of body weight or about 3.50 gm. for a man weighing 70 kg.

6. Both forms of DL-methionine are apparently equally utilized by animals and by man.

7. DL-methionine has been found to be a useful agent for the treatment of hepatic cirrhosis. The recommended daily dose is from two to five gm.

8. Numerous natural foodstuffs of plant origin, rich in protein, have been shown by chemical and biological assays to possess low biological values as a result of their low methionine content. The biological values of these foods could be enhanced by methionine supplement.

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Acute Amebic Dysentery

By

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Acute amebic dysentery is a rare event in amebiasis, or infection by Entameba Histolytica, and is characterized by frequent dysenteric stools containing blood and mucus, in which abundant amebae are usually found without difficulty. The dysenteric syndrome, contrary to current acceptances, is very uncommon, and the idea that it is common has arisen from reports emanating from hospitals to which the more acute cases naturally are sent, and where the chronic disease seldom is seen, except when a case comes in for a check-up. In the chronic cases, the etiology usually is missed, since, in the absence of acute diarrhea, the stools are not subjected to adequate examination. Then, again, certain non-pathogenic amebae, or even mucosal cells sometimes are

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mistaken for E. histolytica through lack of knowledge of this organism. Finally, I find that most physicians are insufficiently aware of the distinct difference in symptomatology between amebic and bacillary dysentery.

Bacillary dysentery, as well as other diarrheas, are frequently mistaken for amebic dysentery, but it should be borne in mind that an epidemic of amebic dysentery is never likely to occur. Manson-Bahr refers to this point, and states that in the Gallipoli campaign of World War I, it led to grave consequences for the patients. Wenyon has expressed a belief that the famous Chicago epidemic of 1933, which was traced to a hotel, was actually an epidemic of bacillary dysentery in persons in whom the E. histolytica carrier rate was high. In Palestine, amebic dysentery was diagnosed much too frequently until it was understood that the majority of the cases were of bacillary origin. Many physicians were in the habit of administering emetine in every case of protracted diarrhea without sufficient etiological investigation. Chronic amebiasis in Palestine, and presumably in other countries, is at least ten times as frequent as the acute intestinal manifestation.

In this paper, while I do not attempt to indicate that profound difference, either in pathology or clinical findings, exists between the two forms of dysentery, I desire to show that there are special features which permit clinical differentiation between bacillary and amebic dysentery. Careful study of the patient's history and his complaints should arouse strong suspicions as to the nature of the diarrhea from which he is suffering.

The report is based on a thorough investigation of 35 cases of true amebic dysentery which occurred in Palestine in different localities and at different times. All were adults between 20 and 56 years of age, the majority being between 30 and 40. In nine cases the attacks came on without any previous history of abdominal distress. The others gave the usual history — slight attacks of diarrhea, alternating with constipation, severe gaseous distention, and so on. In four cases, dysenteric disturbances had been noted several months previously. In all these 35 cases there was a relative feeling of well-being in spite of large numbers of evacuations, and they were all able to work, thus conforming to Manson-Bahr's conception of "walking dysentery." Many of them waited a week or more before consulting the physician and the diarrhea, in the absence of therapy, continued for two weeks or longer with from five to 10 evacuations per day. In no instance did *fever* occur. In only one case, which ended in death, the temperature rose conjointly with the appearance of signs of peritonitis. It is remarkable that the appetite usually remains good. The patient often says: "My appetite is fine and I feel excellent." The tongue is clean. When anorexia accompanied by nausea appears, a complication subsequently is found, usually in the liver. One patient with dyspepsia was in the beginning of pregnancy, and two suffered from duodenal ulcer. Pain if present, is insignificant, except for colic before evacuation, and there is no abdominal tenderness. Slight tenesmus may be noted. The stool is soft, chocolate-brown in color, and mixed with mucus and blood. When clear mucus appears, it is darker in shade than the mucus seen in bacillary dysentery. In cases without any preceding abdominal history, all symptoms subsided after the first injection of emetine. In those cases in whom there had been a previous history of abdominal distress or diarrhea, only slight amelioration of symptoms was effected after three to four injections of emetine, and pains persisted, appetite did not return, weakness remained, and dysenteric attacks recurred. Emetine was followed by Yatren, 1.5 grams daily for two weeks. Two brief case reports are submitted:

Case 1. H. L., a woman of 25 years of age. Two weeks previously, sudden diarrhea with mucus and blood, and as many as 10 evacuations daily began, although she had never previously had abdominal symptoms. She was without pain, appetite good and general feeling excellent. A stool examination showed abundant, free Entameba histolytica in rapid motion, and containing erythrocytes. Abdominal examination was negative. After the first injection of emetine, the diarrhea ceased, and never returned, and she was well three months later.

Case 2. Ch. A., aged 39. History showed severe diarrhea four years previously and for several years mild diarrhea alternating with constipation and some minor abdominal pain. The abdomen was severely distended and he complained of nausea, anorexia, tenesmus and general weakness, but has continued working in spite of a severe bloody diarrhea the previous week. The upper abdomen was tender and the tongue coated, and the liver, though not enlarged, was sensitive to fist percussion. E. histolytica were found in the stools. Even after three injections of emetine, he still had three or four daily evacuations, but the stools looked better. He continued ill after three weeks of treatment with the organism still easily found in the stools.

Analysis of the symptomatology: The symptomatology of amoebic dysentery is easily understood when we remember that the process in the uncomplicated case is strictly localized. This is the reason for the lack of generalized response; general good feeling, no fever, no leucocytosis, no symptoms from the upper abdomen, only local pains. Only when the parasites invade the deeper layers and give rise to inflammation of the peritoneum, or if they are swept with the blood stream into other internal organs, especially the liver, do general reactions occur. It is interesting, to note that even diarrhea persisting for a week or more does not give rise to notable weakness, whereas a patient suffering from bacillary dysentery with many evacuations feels bad and weak after a short time. This lack of reaction should attract attention to the specific etiology.

The two cases described above are given as samples for two different disease patterns. In the first, the disease was not preceded by any abdominal disturbances. While in good health the patient suddenly had a dysenteric attack. These are the cases in which the influence of emetine is wonderful indeed. The disturbances pass immediately and no signs of irritability of the bowels remain. These facts suggest that the process is not only localized, but it also did

not burrow deeper which means that it did not give rise to destruction of tissue and certainly did not produce metastases. I feel that these are instances of recent infection which gave rise, for an unknown reason, to a strong early reaction. The process is certainly still superficial, and it seems that emetine will only then reach the amoebae. This conception conforms with the opinion of those who maintain that emetine does not help when the amoebae are localized in the deeper layers of th bowel wall (Chopra). This is evidently the reason why emetine is apparently of no help in the cases of the second kind, which represent instances of chronic amebiasis with dysenteric exacerbations. An unspecific action on the mucous membrane of the intestine may also be considered.

Because of the above reasons, should the field of application of emetine which has been limited to dysenteric attacks and secondary amebiasis be further narrowed, by taking out the dysenteric attacks of chronic amebiasis? Because of the toxic properties of emetine we should try to define strict indications, and apply it only where it is known to be efficient.

The dysenteric reaction must be understood as a complication and, as already stated, a rare one. According to Acton, it is encountered in only 5% of all infected. Manson-Bahr met only four among 535 cases, and Canaan found cases of amoebic dysentery very rarely even in Palestine (Arabs only).

We should now seek the cause of this dysenteric reaction. With this question we enter into the complex pathology of amebiasis. But here is not the place for detailed discussion of these unsettled problems. I only intend to give some hints.

The dysenteric reaction is dependent in part on the condition and the constitution of the infected person, and in part on extraneous factors. The higher age (56) of the one fatal case, in conjunction with his bad general condition, is surely to be blamed, at least partly for, the severity of his illness. According to Alexander and Meleney, lack of Proteins and Vitamins does not cause a greater infection rate, but more disturbances. Europeans suffer more than natives (Gurwitz-Tiberias), because of diminution of general resistance, or perhaps due to a lack of immunity. Surely the sensitivity of cultured people and their ability to express their feelings also play an important role in determining the symptomatology, especially of abdominal disturbances. Generally, the graver forms of amebic infection are most frequent in tropical countries. In our cases, there was no apparent cause for the dysenteric reaction. All the patients were well nourished and healthy, and the attacks occurred in winter as well as in summer.

Of course, the idea is appealing that the dysenteric attack is caused by a more virulent strain of Entamoeba histolytica, or that an apathogenic strain lodging for some time in the bowels, becomes suddenly pathogenic. Until now, however, nobody succeeded in proving the existence of a species or a strain which always gives rise to grave disturbances or always to light ones. It was proved, however, that one strain may cause all conditions, from the healthy carrier state to the gravest illness. So far, we have no evidence for the possibility of a change of virulence.

Because of lack of evidence, some authors want to ascribe differences in the symptomatology of the disease to the interaction of certain bacteria, (Acton, Deschiens). According to these, Entamoeba histolytica is a non-pathogenic parasite and only becomes pathogenic by a change of the intestinal flora. The bacteria concerned are streptococci, B. coli, and especially B. dysenteriae. On pathological grounds, however, and because of the character of amebic dysentery, this opinion does not seem to be acceptable (Meleney and Frey, Faust).

Amebic dysentery is a rare happening in the course of infection with Entameba histolytica (Amebiasis). Erroneously, it is often thought to represent the characteristic picture of amebic infection. Its features differ also from those of bacillary dysentery.

On the basis of 35 cases of amebic dysentery which were diagnosed in Palestine, the characteristic features of this condition are described. These are distinguished by a general well-being in contradiction to the grave dysenteric disturbances. Two cases are described to represent two different types of dysenteric attacks. The first, without any history of abdominal disturbances, whose illness began with the dysenteric attack. In the second, the diarrhea represents only an exacerbation of a long drawn chronic process. In the first, all the symptoms and signs of the disease passed after one or two injections of emetine, and did not recur.

The first is thought to originate from a recent and still superficial infection, which, because of some unknown reason, gave rise immediately to a dysenteric attack. The cases of the second type were influenced very little by emetine. This observation should narrow the field of indication of emetine still further.

The cause of the dysenteric reaction which should be understood as a complication of amebiasis, is not clear. It is dependent on the one hand on the patient's condition and on the other hand perhaps on special qualities of the parasite or on the influence of bacteria lodging in the intestine.

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A Consideration of Certain Sources of Error in the Positive Diagnosis of Gastric Carcinoma

By

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IT IS QUESTIONABLE whether the removal of a non-cancerous stomach is in retrospect justified by an uncertain diagnosis of gastric cancer. Zeal for improving the surgical cure rate of carcinoma of the stomach by attacking earlier lesions is misdirected if diagnostic criteria are relaxed beyond a certain point. There is a responsibility to abstain from surgery on the normal stomach, as well as a responsibility to remove the malignancy as soon as possible. But unfortunately, however commendable such thoughts may be, certainty of diagnosis must necessarily decrease with diminished size and age of the lesion, and several moral and practical factors encourage surgery when there is a certain reasonableness of suspicion of malignancy.

On the one hand, there is the omnipresent professional cancer-phobia, with its drive to catch the cancer in a curable stage, plus the realization that, since the pathologist often cannot determine whether a resected stomach contains a malignant lesion until histologic studies are made, the clinician can hardly presume to make a positive diagnosis of no cancer. For this latter reason, the surgeon who has decided to operate feels obliged to resect, even though the stomach at operation appears normal grossly — if the earliest lesions are to be cured, the matter must not be decided at operation. Once the preoperative diagnosis of cancer has been decided upon, the immediate clinical problem has resolved itself — diagnostic errors which may be revealed can be reviewed later. Although it may be true that certain gastric lesions which are easily misdiagnosed as early carcinoma are also best treated by resection, it is not permissible to excuse a diagnostic error on such grounds.

On the other hand, when a patient is submitted to gastrectomy, he is submitted to an operative risk, he receives a total vagotomy below the line of resection, he is from that time to some extent a gastric cripple, and he stands a rather poor chance of being cured of any malignancy which might be present.

The problem takes on several aspects. There is the problem of the patient, referred with the positive diagnosis of gastric malignancy, who after appropriate investigation appears to have no malignant disease. There is the patient in whom repeated X-ray or gastroscopic examinations by one examiner give varying impressions regarding the presence of tumor, and the patient in whom X-ray and gastroscopic opinions lead to discordant diagnoses. In any of these situations the best clinical judgment may necessitate resort to surgical treatment — the remark that the best diagnosis is not necessarily the correct one was more than a quip.

There are reported here data in the cases of several patients who presented difficult diagnostic problems in the field of early gastric carcinoma, patients in whom the demonstrable abnormalities suggesting tumor were interpreted at different stages of investigation as probable or positive indication for gastric resection, and in whom final analysis indicated the absence of tumor. By assembling this data it was hoped that some tendency might be found which would allow a better understanding of the causes underlying the diagnostic errors involved. An important sidelight would be an evaluation of the oft-mentioned concept of the "complementary diagnostic roles of the radiologic and gastroscopic methods."

MATERIAL

The 28 patients presented were white male military personnel studied at Walter Reed General Hospital, a Tumor Center, by a rather closely-knit diagnostic and surgical staff. The Army set-up assured diagnostic teamwork, which, in turn, assured a conservative approach: although there were often differences of diagnostic opinion, no patient was operated upon unless there was concerted approval of the radiologic, gastroscopic and surgical staffs, as well as unanimous written approval of a Tumor Board composed of the chiefs of the hospital services. Some of the patients were admitted directly and initially studied here and others were referred from other Army hospitals with transfer diagnoses

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of gastric carcinoma of varying degrees of certainty. All patients were at some time incorrectly diagnosed as having carcinoma of the stomach. The error of the diagnosis was proven by the study of the resected stomachs in 11 patients (Group 1), and recognized without surgery by the combined opinions of all examiners in the cases of 17 patients in whom operation was decided against (Group 2). Thus, in Group 2 the final diagnoses, which are used for comparative purposes herein, were not proven histopathologically. The final decison was rendered in each case within a period of three weeks of admission to this hospital; the problem of each diagnosis was considered to be a static one — a period of observation for the purpose of demonstrating a changing picture has not been considered proper management in this tumor center. It was often found necessary to repeat certain examinations several times before a proper decision could be reached. Thus, an average of 2.9 gastrointestinal X-ray examinations and 3.2 gastroscopies was done per patient.

RESULTS (See Table)

Location of questionable area. The antrum was the region most frequently involved in diagnostic error. Among the 28 cases, the mistake was made in the interpretation of antral findings in 19. The greater curvature of the pars media presented the difficulty in five cases, the lesser curvature of the pars media in three, and the fundus in one. The same relative proportions hold when the figures are broken down into the resected and non-operated groups.

Lesions mistaken for carcinoma. The final diagnoses included 12 cases of chronic hypertrophic gastritis of the antrum, six of benign gastric ulcer, five normal stomachs, two chronic superficial gastritis of the antrum, and one each of benign adenoma, gastric syphilis, and more generalized chronic hypertrophic gastritis.

Types of lesion upon which operation was resorted to. In the series considered here, all cases of gastric ulcer were resected, not because it has been the policy to remove all gastric ulcers, but because they were mistaken for carcinoma. Of the 15 patients whose stomachs were found to be diseased merely with one of the chronic gastritides, however, only two were submitted to operation. In one of the five patients with normal stomachs, the correct diagnosis did not become evident until the resected specimen had been examined.

The diagnostic efficiencies of x-ray and gastroscopic methods. It is notable that in only one case of this series did both roentgenologist and gastroscopist make the diagnosis of carcinoma. One or the other method revealed no evidence of malignant disease in the remaining 27; nevertheless, in 10 of these the findings suggesting carcinoma, as demonstrated by one method alone, were felt valid enough to warrant gastric resection. At some time during this study, an incorrect diagnosis was made roentgenologically in each of 23 patients, and gastroscopically in six. Of the patients who were submitted to operation, the X-ray diagnosis was wrong in seven and the gastroscopic in five; one of the latter proved to be a normal stomach and another simple chronic hypertrophic gastritis. A large proportion of the X-ray errors (14 patients) was due to misinterpretation of deformities produced in the antrum by one of the chronic gastritides. Gastric resection indicated that the X-ray differentiation of benign ulcer from ulcerated carcinoma had been less accurate than the gastroscopic.

DISCUSSION

Efforts in the clinical investigation of gastric cancer have been directed largely toward the avoidance, at all costs, of overlooking an early lesion. Many studies have considered this, the negative side of the problem, and the results must be eventually a better control of the disease. But needless resection of a stomach as a result of diagnostic error must also be considered a disease to be avoided. This is not a popular point of view where cancer is concerned. Although over-diagnosis of gastric cancer may, in truth, be more commendable than under-diagnosis, both attitudes are to be avoided.

There are only two methods for the positive diagnosis of gastric cancer prior to operation — radiologic and gastroscopic — and no other test gives much specific information. It is probable that methods for cytologic examination of the gastric contents will in the future offer helpful diagnostic information in certain cases. It has become rather trite to point out that gastroscopy and roentgenography are complementary methods for examination of the stomach, and that there are valid practical objections to comparisons of relative diagnostic efficiencies. When, however, the problem of elucidating causes for diagnostic error arises, it is essential that the sources be uncovered. The practical demonstration of the methods' complementary function was an important result of this study. The diagnostic errors were correlated in a remarkable manner with the failure of the methods to back each other up. In only one of the cases did the X-ray and gastroscopic diagnoses of cancer agree; the error was suggested although not recognized in ten who came to operation. By repeated examinations the errors in the other 17 became evident. The serial gastroscopic studies in any one patient, particularly among the group with antral gastritis, were helpful in convincing the examiner, as well as the others concerned, that no malignancy was present. At the risk of offending the professional mind, it must be pointed out that independence of diagnostic decision on the parts of the various examiners must necessarily pay important dividends. Although somewhat paradoxical, it has been found that the closest cooperation between radiologist and gastroscopist — and, therefore, the greatest diagnostic accuracy — stems from a mutual

TABLE I

Data on 28 patients in whom an erroneous diagnosis of gastric carcinoma was made.

	GROUP 1 Patients diagnosed as ca, operated on, no ca found.		GROUP 2 Patients in whom ca suspected, operation decided against, final Dx: no ca.	
Number of patients	11		17	
Gastroscopic Dx of ca wrong	5			
X-ray Dx of ca wrong	7			
Gastro. and X-ray Dx of ca wrong	1			
Gastro. Dx suspicious of ca			1	
X-ray Dx suspicious of ca			16	
Both suspicious of ca			0	
Location of region in question				
Antrum	7		12	
Great curve pars media	2		3	
Lesser curve pars media	2		1	
Fundus	0		1	
Pathologic diagnosis	**Gastro:ca**	**X-ray:ca**		
Normal stomach (1 case)	1			
Benign ulcer (6 cases)	2	5		
Chronic hypertrophic gastritis (2)	1	1		
Benign adenoma (1)	1			
Gastric syphilis (1)		1		
Final diagnosis (clinical)			**Gastro:ca**	**X-ray:ca**
Normal stomach (4 cases)			1	3
Chr. hypertrophic antral gastritis (10)				10
Chr. superficial antral gastritis (2)				2
Chr, hypertr. gastritis, general (1)				1

friendly skepticism of the other's diagnosis. It is not enough that an effort be made to avoid reading the findings of one into the picture as it is seen by the other. By correlating the discrepancies, some therapeutic errors may be avoided. The X-ray or gastroscopic diagnosis of "I don't know" is often a commendable one. Moersch (1) has summed up these matters well from the endoscopist's point of view: "All too frequently, an attempt is made to establish a definite gastroscopic diagnosis by a single examination. When there is a question of doubt, it is well to employ the Taylor 'two-look' technic, and especially to emulate the roentgenologists, who have learned by experience that much may be learned by repeating an examination once, twice, or even more times. "Latter he added (2): "It has been my observation that a frequent cause for error in gastroscopic diagnosis is an attempt to have the gastroscopic findings correspond to the clinical history."

Two questions immediately arise out of the data presented here: how many early gastric carcinomas were not detected or suspected in other patients studied during the same period, and what will be the cure rate in those patients who were correctly diagnosed as early carcinoma and treated surgically? The more general corollary question is: in view of the diagnostic difficulties involved at what point do operative risk and post operative morbidity properly preclude earlier and, diagnostically, less certain attempts to remove gastric carcinoma? It would be important to know the answers, but none can be given at this time. It is apparent that the series presented here demonstrates that there can be many mistakes even when a conservative attitude governs the thinking in team diagnosis.

SUMMARY AND CONCLUSIONS

1. In spite of repeated X-ray and gastroscopic examinations, as well as a diagnostic attitude of skepticism and caution, an erroneous diagnosis of carcinoma of the stomach led to needless gastric resection in 11 patients.

In 17 other patients an incorrect diagnosis of gastric cancer was made, but the error was detected and operation avoided by additional X-ray and gastroscopic studies.

2. Chronic antral gastritis was the disease most frequently mistaken for carcinoma.

3. Because in only one of the 28 misdiagnosed cases did the roentgenologist and gastroscopist agree on the diagnosis of cancer, the study emphasizes that an X-ray: gastroscopic discrepancy must engender serious doubt as to the presence of a malignant lesion.

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NUTRITION

Effects of Bone Meal on Oral Structures in Pregnancy

By

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IN THE PAST, many erroneous ideas were held concerning the effects of pregnancy on the oral structures of pregnant women. The old legend, "a tooth for every child," was believed by many physicians and dentists, as well as by the laity, with the result that oral health was neglected at a time when it should have received special attention. Today, fortunately, this is not the case. A review of current literature shows that the mouths of cooperative pregnant women now receive the care which they deserve.

Interest in the field of dentistry for pregnant women has only developed within the past decade. Prior to 1939 little was written on the subject. The research of such men as Schour (1), Bear (2), Bahler (3), James (4) and others, and the work of a host of histologists, pathologists, and physiologists have unearthed a wealth of material.

Gross endocrine imbalance due to pregnancy and a faulty diet may affect the oral structures, but these disturbances are rare and generally affect the body as a whole. Are oral disturbances any more common in pregnant women than in non-pregnant? With the single exception as shown by Cahn (5), a transient pulp hyperemia is likely to occur in the early months. This hyperemia is only a temporary condition with absolutely no after-effects. Is the formation of new caries greater in pregnant women than in the non-pregnant of the same age? According to some authors, it is retarded, while others believe that pre-existing caries may be aggravated in pregnancy, and this advance made more rapid.

When once fully formed, the teeth can not be changed except by external factors. Unlike bone, the teeth do not serve as calcium stores, and can not be called upon to meet physiological needs. Enamel is non-vital, and does not enter into the picture. Dentin, however, is vital, and may be affected by a calcium deficiency. When first formed, dentin is a collagenous matrix which later calcifies. Since dentin is formed by pulp continuously throughout life, with increased local formation responding to caries or other local stimulation, a lack of calcium may result in a weakened dentin layer. With the exception of pre-existing caries, as mentioned above, this effect is without consequence because the tooth at this time is already fully matured. Cementum is never affected by pregnancy. Only pathological lesions such as abscesses can cause the resorption of cementum or the tooth root.

A calcium deficiency may affect the bony structures of the mouth in a more serious manner. In an acute deficiency, the jaw bones, like other bones, may be called upon to release some of their calcium. In that case, the teeth will lose their support, and consequently, although perfectly sound, may be lost. This so-called periodontal disease, not always caused by deficiency is common in middle-aged people. Although theoretically possible, it is not particularly manifest during pregnancy.

Other studies have shown salivary changes during pregnancy. In some women there is an increased salivary flow of a slightly more acid saliva. Here again, however, no harmful sequellae have been observed. The condition of gingival hypertrophy of pregnancy, of little note, is due to metabolic disturbance, and tends to disappear after delivery.

The above discussion intimates that pregnancy has little effect on the dental health of the mother. The dentition of the fetus, however, may be vitally affected by the mother's diet. Such a study has been undertaken and recently reported by Toverud (6) who used medication similar to our controls. No bone meal was used. "A comparison of children coming under control after the first year of life with those controlled from birth showed a 50% reduction in the incidence of dental caries in the latter group."

One allied subject remains to be discussed: that of dental care during pregnancy. Most practitioners are confirmed in their belief that any sound conservative treatment may be undertaken. Root canal therapy and extensive surgery should not be attempted during the last few weeks. Common sense and a careful study of the patient should dictate the procedure to be followed.

We are presenting here clinical observations made upon 250 cases of women pre- and postpartum. Of these cases, we have 250 recorded dental reports of the patients' first visits and 114 follow-up dental reports. Only the latter cases are included in this presentation The 114 cases are sub-divided into two groups 50 con-

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trols cases and 64 cases using meal.

The plan of procedure was as follows:

1. In the usual prenatal instructions to the patient on her first pre-natal visit, special emphasis was placed on dental care, and the patient was referred to her dentist with the following letter:

Re:

Dear Doctor:

Will you kindly mail me a report on the above named patient stating the following:

Number of fillings
Number of loose fillings
Number of cavities
Gum erosion
Epulis
Tartar
Condition of enamel
Estimate general condition of mouth as poor, good, excellent.

Many thanks for your thoughtful cooperation.

Sincerely yours,

a. A special notation was made on the obstetrical record. The patient was reminded to get her dental report each prenatal visit. We were successful 250 times.

b. If the dentist failed to reply, the duplicate of the letter given to the patient was sent direct to his office.

2. Postpartum — a letter was sent to the patient stressing the advisability of a dental recheck. If there was no response to this, a final "this is urgent" letter followed asking for her cooperation in continuing the good care received during pregnancy.

a. An additional letter was sent to the dentist, enclosing a special form to be filled out and returned to us, and a stamped-addressed envelope to be mailed to the patient with her appointment card. We felt that "two-way" pressure to make the patient dental conscious woud be more effective. We were 50 per cent successful.

3. In all— two follow-up letters were sent to the dentist.

a. In the first, already mentioned above, the dentist was asked to recheck the condition of the patient's teeth postpartum, and state, on the special form enclosed, whether, in comparison to his examination during the early prenatal months, the teeth showed:

Check one	Yes	No	
	()	()	(1) Tendency to increased cavitation
	()	()	(2) Loosening of fillings
	()	()	(3) Deterioration of enamel
	()	()	(4) Increase of erosions
	()	()	(5) Increase of gingival caries
	()	()	(6) Loosening of teeth in sockets
			(7) General condition of mouth

114 dentists replied to the first postpartum checkup.

b. In order to get unbiased dental observations the following letter was sent:

Re

Dear Doctor:

You have been very thoughtful in your cooperation in reporting the general condition of the mouth of your patient before and after pregnancy..

She has had calcium and vitamins, bone phosphates, products containing fluorine, etc.

Do you think her mouth condition improved while she took the medication?

What has been your experience as to the value of calcium, fluorine, bone phosphates, etc, as regards the dental condition of your patients in general — (1) when not pregnant and (2) when pregnant?

I am enclosing a blank sheet of stationery and a stamped return addressed envelope.

An early reply as to your conclusions would be appreciated.

Sincerely yours,

Out of 250 cases, only 114 could be followed up properly.

The reasons for the failure of 50% of the cases to cooperate were given as follows:

1. Broken dental appointments: (Patient could not leave baby. Too busy with household duties)
2. Difficulty in getting new or old appointments with shortage of dentists.
3. Non-cooperation of patient.
4. Lack of special interest by dentist.

The medication given to the patient was:

50 cases Controls	Special Capsule
Unicaps (Upjohn) (one, night and morning)	Unicaps (Upjohn) (one, night and morning)
5000 A	
500 USP units Vitamin D	
37.5 mgm. Ascorbic Acid	
2.5 mgm. Thiamin Chloride	
2.5 mgm. Riboflavin	
0.1 mgm. Pyridoxine Hydrochloride	
5 mgm. Calcium Pentothinate	
20 mgm. Nicotinamide	
Dicalcium phosphate and Viosterol (Squibb) 64 cases	Bone Meal Caps. VIIss grs Capsules
Dicalcium Phosphate gr. 4.5	(one, night and morning
Calcium Gluconate gr. 3	for 4 days)
Vit. D 330 USP units (derived from Viosterol)	
Cal-C-Tose (Roche)	
Each dose, 2 heaping teaspoonfuls	
2000 USP units Vitamin A	
0.5 mgm. B_1	
0.5 mgm. B_2 (Riboflavin)	
50 mgm. C	
500 USP units D	
Calcum and Phosphorus (quantity not stated)	

Where indicated, both series were given. Additional Vitamin C upon the dentist's request, and Parenteral liver injections — 10 to 15 units — to combat severe anemia. severe anemia.

The percentage results of oral examination by 114 dentists are as follows:

Evaluation of the above data indicates:

Less cavitation with Bone Meal	12%
Less deterioration of enamel with Bone Meal	6
Less erosions with Bone Meal	11
Less loosening of fillings	7

Thus we see that Bone Meal benefited the oral struc-

Results of examination of mouth:	Control 50		Special Bone Meal 64	
	Yes	No	Yes	No
Tendency to increased cavitation	18%	82%	30%	12%
Loosening of fillings	5	95	12	7
Deterioration of enamel	13	87	7	6
Increase of erosions	20	80	11	11
Increase of gingival caries	7	93	7	93
Loosening of teeth in sockets	5	95	4	96

tures of the mouth by 36%. There was no increase of gingival caries or loosening of teeth in sockets, but an occasional case of hypertrophy in each series.

The general condition of the mouth was evaluated as follows:

	50 Control	64 Bone Meal
Excellent	2%	10%
Very Good	2	5
Good	57	44
Fair	22	25
Poor	8	1
Better	1	1
Normal	0	1

In general the gradations of clinical conditions of the oral structures may be summed up as:

Excellent ------ Bone Meal 8% better than controls
Very good ... Bone Meal 3% better than controls
Good Controls 13% better than Bone Meal
Fair Bone Meal 3% better than controls
Poor Bone Meal 7% better than controls

All in all, the balance is in favor of Bone Meal even though all the patients were dental conscious On a percentage basis there was improvement of approximately 21% in oral condition when Bone Meal was used.

The 93 dentists summed up their experiences as follows:

Definitely improved with Ca, F, etc. -------- 12 - Good
Decreased susceptibility to caries -------- 11 - Good
In both pregnant & non-pregnant, including Ca, F lessens caries promotes firmer gums, harder tooth structures ---------- 2 - Good
Medication and care of mouth keep teeth and gums healthy ---------- 13 - Good
Calcium affects alveolar process -------- 1 - Good
Excellent supplements to diet ---------- 2 - Good
Functional disturbances in pregnancy increase caries Ca, F helpful ---------- 1 - Good
When pregnant, Ca, bone phosphates, etc. necessary ---------- 1 - Good
Medication more valuable to fetus than to mother -- ---------- 3 - Good
No signs of degeneration of teeth -- 4 - No opinion
Use of F locally too new, but seems to help general health ---------- 5 - Doubtful
Mouth didn't hurt any, so from that standpoint medication worthwhile ---------- 1 - Good
Patient's neglect increases caries, tartar, etc. -------- ---------- 8 - No opinion
3-months check up by bite-wing x-rays valuable to note early decay ---------- 2 - No opinion
"Tooth for every pregnancy" is so much hog-wash -- ---------- 1 - Doubtful
Large cavities become worse during pregnancy ------ ---------- 1 - No opinion
Medications useless in exposed cavities ---------- ---------- 2 - Doubtful
Tooth structure of adults not improved by Ca, F etc. ---------- 1 - Doubtful
Non-pregnant women would benefit by Ca, F, etc. -- ---------- 4 - Good
Public inadequately informed: nourished through ignorance, indifference, or misunderstanding ---------- ---------- 3 - Doubtful
No honest opinion except theory that Ca, P supposed to do good ---------- 3 - Good
Regressions of oral tissue ---------- 2 - Doubtful
Ca, etc. unnecessary expense; gone overboard ---- ---------- 1 - Doubtful
Alkalization by dentifrice, proper brushing, etc. valuable ---------- 2 - No opinion
Limited few never took enough Ca, etc. Therefore no noticeable improvement ---------- 1 Doubtful
Mouth condition excellent before, during and after pregnancy. Therefore, medication inconclusive ---- ---------- 3 - Doubtful
18 years experience: (1) A clean tooth less vulnerable to decay. (2) Vitamins and minerals can't affect formed tooth structure ---------- 1 - Doubtful
General opinion of literature: Little change during pregnancy. "Tooth for every child" is but a poor excuse for dental neglect---------- 1 - Doubtful
to do good ---------- 3 - Good
No decided improvement in mouth either before or after pregnancy ---------- 1 - Doubtful
TOTAL 93

Opinions of dentist as to use of medication:

54 - Good	58.06% -	approximately 58%
22 - Doubtful	23.66 -	" 24%
17 - No opinion	18.28 -	" 18%
		100%

Thus, we see that unbaised clinical dental opinion favors the use of calcium, phosphorus, and vitamins in 58 per cent of cases.

CONCLUSION

1. Of 93 dentists in private communications, 58 per cent favor the use of some form of calcium, phosphorus, flourine, and vitamin D.
2. Bone Meal gives better results by 36 per cent in its effect on the oral structures in pregnancy.
3. The evaluated data indicates that the use of simple Bone Meal without adjuvants is an advancement in therapy.

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(Special thanks to James L. Dannenberg for his thoughtful cooperation)

Volume 16
Number 7

Nutrition Notes

Food Conscious America

There never was a time in the history of this contry—or of any other—when so much interest has been evinced in the subjects of food and nutrition. Newspapers routinely carry columns of information with respect to nutrition, approaching the subject from almost every conceivable angle. Publishers can scarcely obtain a sufficient number of manuscripts to satisfy the public craving for more-or-less scientifically written volumes on health and food. Many governmental departments and bureaus retain hundreds of experts and statisticians and periodically release authoritative information on such subjects as food markets, school lunches and particular studies in nutrition. Some 600 organizations now conduct or support food and nutrition research. There are over 5000 professional personnel now responsible for the conduct or direction of food or nutrition research (Survey of Food and Nutrition Research by the Food and Nutrition Board of the National Research Council). The consolidation of the research work and workers in this special field into a central registry will serve to minimize duplication of subject matter, wastage of many man-hours of professional research personnel and inadequate coverage of research needs. (Nutrition News Letter, U.S. Dept. Agriculture.)

Not only the Federal, but most of the state governments are now vitally interested in what the people eat. Below this level, there are uncounted organizations of civic type active in providing improved foods for children and adults and in inculcating some of the basic and essential truths with respect to human nutritional requirements.

Patients, whom we interview in our consulting room, are, as never before, calorie-conscious. Many of them disturb us by the confidence they repose in their smattering of knowledge. Years ago we reached the stage where it required courage to omit the vitamin prescription. Now we are at the point where it is easier to hand the patient some kind of diet sheet than to explain why we failed to do so.

Yet we naturally welcome the intense interest in food and nutrition. Already the intelligent and well-read patient fully understands that he does not need artificially-provided vitamins if he is receiving a diet high in protein with sufficient calories and protective foodstuffs. Today it is quite possible to avoid embarrassment with respect to "special" diets, particularly with well-informed patients, since they know that the use of restrictive regimes are to be deplored except in particular instances.

The clamor for food information fortunately cannot be capitalized by special interests to any considerable extent, as was the case with vitamins. Physicians generally regard the "crescendo in food facts and fancies" as salutary. On the whole the attitude of the science-hungry public augurs well, in the long run, for a still more vital populace. It is a "down-to-earth" attitude quite in keeping with our culture of superactivity. If a physician places a book of poems beside a book on food in his waiting room, he will find the latter constantly used and the former almost never.

Whither America? To more and better food for all its citizens in the name of health and strenuous life!

Labile Diabetes

Especially in young persons with diabetes mellitus it is all too common to encounter the troublesome condition which has been variously termed, "labile", or "unstable" or "brittle" diabetes. In such cases it often becomes practically impossible to avoid insulin reactions on the one hand and heavy deposits of glucose in the urine on the other hand. The patience and skill of the physician is overtaxed and the morale of the patient impaired by the impossibility of stabilizing the dietary level and the insulin dosage. Free dieting with a conventional daily dose of insulin is not successful, because the reactions of these patients, while clinically conforming to the hypoglycemic type, do not always occur in the presence of a low blood sugar and may, indeed, appear while the blood sugar is comparatively high. Such cases ought to be differentiated from those in whom the "insulin" reaction is cured by the administration of excess carbohydrate. The term pseudohypoglycemic has been suggestel by Fabrykant and Pacella (1) for those cases in whom the blood sugar is high during the reaction and for whom the administration of excess carbohydrate provides no help. A study of seven cases of labile diabetes revealed abnormal encephalograms in six of them and it is remarkable that, in these six cases, the reactions (pseudoglycemic, especially) were largely controlled by the administration in appropriate doses of the anticonvulsants, dilantin and mesantoin. The biological value of this finding appears to be rather important and, as Himwich (2) has suggested "hypoglycemic" reactions may result from a low brain sugar which may not be reflected in the systemic blood.

1. Fabrykant, M. and Pacella, B. L.: Labile diabetes: electroencephalographic status and effect of anti-convulsant therapy. Ann. Int. Med., Nov. 1948, Vol. 29, No. 5, 860-877.
2. Himwich, H. E.: Discussion. Proc. Ann. Diab. Assn., 1948. VII, 243-244.

Metabolic Hide and Seek

We have heard that rats live longer on a regime of periodic fasting, yet it is certain that they would not adopt such a regime in the natural state unless through force of circumstances.

In human society a few individuals (who probably have not heard much about the rats) imitate their laboratory behavior under the name of freedom.

The "free-lance" eater eats whats he wants, when he wants it. He may be said to devour precisely what he craves at the exact moment of desire. His alimentary pattern defies normal routine. Breakfast may be

Welch rarebit or supper, oatmeal porridge. The size of a meal may vary from a teaspoonful of caviar to a joint that would have discouraged Henery VIII. He may pass two or three days without food of any kind. Should he be a guest at your home, he explains that he eats only when hungry, after the example of lions.

He should not be married for he is, at heart, a libertine. Foraging in the refrigerator at 3 A.M., sitting inert at a banquet at $5.00 per plate, arriving at restaurants at *a la carte* hours, remaining unmoved by his wife's culinary *piece de resistance*, then mouthing dried raisins an hour later — such actions betoken the social misfit, — the human rat.

With determination he pursues a unique and disturbing course and is imbued with its alleged reasonableness. To him, all other men belong to the uninitiated. Persons who sit down to three formal meals a day are regarded as stupid, stuffed and stereotyped. Some magic essence appears to bud in the catabolic periods and flower in the moment of alimentation. His smile is a sign and pass of a secret order who do not proselytize, but are content in emptiness or fullness to regard the generality with whimsical compassion.

Yet most of these freedom-loving citizens are intellectuals. Have they stumbled upon a valuable secret? Are they merely compensating for the hum-drum of professional duties, the boredom of daily routines, the pressure of taxes, the irksomeness of the proletariat and the pure cussedness of human life? What does it matter? The disease is not contagious.

Abstracts on Nutrition

TRAUT, E. F. AND MATOUSEK, F. L.: *The relation of ascorbic acid to chronic arthritis.* (Ill. Med. Jour., Vol. 95, No. 1, 38-39).

Inasmuch as there have been hints in the literature that lack of ascorbic acid may play a causal role in the production of chronic arthritis, the authors examined the fasting blood levels of ascorbic acid in cases of hypertrophic arthritis, rheumatoid arthritis and in normal controls and while the ascorbic acid level in the serum of arthritic patients as compared with other patients was low, no significant difference was noted in these levels as between hypertrophic and atrophic arthritis. The serum level of ascorbic acid was higher in 7 private patients than in 11 clinic patients. Restoring the serum level to 1 mg. per cent had no appreciable effect on the chronic arthritis. Naturally, however, it is a good hygienic principle to restore low levels of serum ascorbic acid to normal, but not with the anticipation that any improvement in the arthritis will result.

HALL, B. E. AND CAMPBELL, D. C.: *Vitamin B_{12} therapy in pernicious anemia. I. Effect on hemopoietic system: preliminary report.* (Proc. Staff Meet., Mayo Clin., Dec. 8, 1948, Vol.23, No. 25).

Eleven patients in relapse, suffering from pernicious anemia were treated with vitamin B_{12}. This product, when administered intramuscularly effectively induces hematopoietic responses. The reticulocyte response and the rate of rise in erythrocyte levels are comparable to those observed when liver therapy is employed. Extremely small doses of vitamin B_{12} are effective. With parenteral administration, approximately 1.0 microgram is the equivalent of 1 U.S.P. unit of extracts of liver or stomach mucosa. Serial aspirations of the sternal bone marrow have shown that erythrocyte regeneration from megaloblastic to normoblastic types of cells may occur in 48 to 72 hours when relatively large amounts of vitamin B_{12} are administered, e.g., 25 micrograms.

BARNES, H. H. F. AND MORGANS, M. E.: *Pregnancy complicated by diabetes mellitus* (Brit. Med. J., Jan. 8, 1949, 51-54).

In the majority of pregnant diabetics, carbohydrate tolerance was found to diminish as pregnancy advanced. In some it increased prior to delivery and possibly the administration of estrogens therapeutically may have been a factor in the improvement. The tendency of the pregnant diabetic to develop hydramnios is confirmed. Hypoglycemic symptoms and hypoglycemic coma tend to occur in early pregnancy and ketosis and diabetic coma in the latter part of pregnancy. The maternal prognosis is good, and pregnancy does not make the diabetes worse provided it is well treated. In a first series of 43 pregnancies, the late fetal mortality rate was 55 percent, but in a second series *in which estrogens were given*, there were only 3 deaths. It is suggested that the factor affecting the viability of the fetus probably arises in the maternal anterior pituitary lobe. The tendency of the fetus to gigantism may be due to an excess of the growth hormone from the maternal pituitary gland.

TUFT, L.: *Allergy as a factor in gastrointestinal disorders.* (Rev. Gastroent. March 1949, Vol. 16, No. 3, 209-217).

The author finds that some patients exhibit an *intolerance* to sugar and fats and this must be distinguished from *allergy*. Diarrhea due to sugar intolerance stops as soon as sugars as such, are eliminated from the diet. So far as allergy is concerned with the gastrointestinal tract, the use of elimination diets are necessary to detect the allergen. Skin tests give erroneous results, inasmuch as a person's skin may show hypersensitivity to a substance which is quite harmless when eaten. When a patient presents symptoms of functional disturbance of digestion one must make sure that he is not dealing with food intolerance, rather than allergy. In the case of allergy, usually one substance, e.g., a protein, is responsible, but in food intolerance, all sugars, or in other cases all fats may be responsible.

DEBRE, R.: *Toxic effects of overdosage of vitamin D_2 in children.* (Am. J. Dis. Child. June, 1948, Vol. 75, No. 6, 787-791).

The author states that in France especially there has been a tendency to overdose children with viosterol, sometimes in cases of primary tuberculosis, pleural effusion or tuberculosis of the skin. The first and persistent symptom of intoxication is anorexia which comes on suddenly, with great weight loss eventually and a mental state sometimes regarded as mental disease. Repeated and frequent vomiting soon appears. Thirst, polydipsia and polyuria with nocturia, headache, pains, and stiffness in the limbs, muscular cramps are other common symptoms. Unless the vitamin is discontinued, severe dehydration and pallor, without anemia, present themselves. Stupor may supervene, and there is often slight fever. Elevation of blood pressure to 130/80, elevation of blood urea and impaired renal function are found on examination. Calcium and phosphorus blood levels frequently are high. Somtimes there is a severe anemia and there is acceleration of sedimentation rate. X-rays may reveal osteolysis of the bones of the feet. Achlorhydria is present and is histamine resistant. Usually on withdrawal of the vitamin all symptoms disappear. In more serious cases, recession is slower, with hypotonia, loss of reflexes, loss of equilibrium and insomnia, and occasionally convulsions. Ten fatal cases have been reported in the past 18 years. The author had 2 fatal cases. Cerebral hemorrhage was present in one. The two chief dangers are renal and cerebral impairment. At autopsy, calcareous precipitates in the renal tubules and changes in the tubular cells, glomeruli and interstitial renal tissues are found, as well as calcareous deposits in the heart muscle, the dura, the lungs, the gastric glands, the synovia and the subcutaneous tissues. A child fully grown should receive not more than 1,000 units a day. Sunshine may cause aggravation. A low calcium and milk diet is needed for recovery.

SCHEMM, F. R.: *Certain clinical aspects of the application of water balance principles to heart and kidney disease.* (Ann. Int. Med., Jan, 1949, Vol. 30, No. 1, 92-99).

In applying water balance principles in renal diseases and in the renal complications of cardiac disease for the correction or prevention of anuria, azotemia and edema the author has found it important to keep in mind: (1) that the increase in the plain-water needs of the body in serious illness is often of great magnitude, (2) that water does not reach the kidneys until all the other demands of the body for water have been satisfied, (3) *that brine is not water.* The sodium laden water of Ringer's, R-molar lactate and Tyrode's solutions, and of ordinary plasma and of blood as well as water of isotonic sodium chloride solutions, should not be counted in the plain-water intake, because their water cannot be satisfactorily used for the metabolic purposes of plain-water.

COLEMAN, P. N.: *Cirrhosis of liver presenting as severe anemia.* (Brit. Med. J., Nov. 13, 1948, 858-859).

Two cases are reported of cirrhosis of the liver in which severe anemia, thought to be hemolytic, was the predominant feature. Hemolytic anemia is considered to be an uncommon complication of hepatic cirrhosis. Usually any anemia associated with cirrhosis is normocytic or macrocytic but without evidence of hemolysis, and is usually not severe. However, cases showing severe hemolysis have been reported in the literature. In the case under description the blood cell morphology bore no resemblance to that of pernicious anemia. Both cases terminated fatally in spite of repeated blood transfusions. The livers showed diffuse cirrhosis.

RATHBUN, J. C.: *"Hypophosphatasia"* Amer. J. Dis. Child., June, 1948, Vol. 75, No. 6, 822-831).

An unusual and previously unreported type of faulty bone development is described in which a low to absent alkaline phosphatase appeared to be the primary defect responsible for the clinical picture. The long bones showed grossly irregular cartilage maturation and lack of calcification. The vault of the skull was almost devoid of calcium. Treatment failed to change the course of the disease, which terminated fatally.

DEAMER, W. C.: *Stimulation of growth in boys by subingual testosterone therapy.* (Am. J. Dis. Child., June, 1948, Vol. 75, No. 6, 850-859).

The author, as a result of clinical tests, believes that until a better method of stimulating longitudinal growth appears, certain prepubertal boys whose bone age is retarded by several years and who are extremely short in stature, may be suitable candidates for sublingual testosterone therapy, provided this is not carried out to the point of undue advancement of the bone age. The method is suitable only to carefully selected and markedly dwarfed boys.

BISKIND, M. S.: *Endocrine disturbances in gastro-intestinal conditions.* (Rev. Gastroent., March 1949, Vol. 16, No. 3, 220-225).

This article is mainly a plea for the use of adequate nutritional measures in case of endocrine disturbances and in gastrointestinal conditions. The author, with G. S. Biskind, found that the liver which inactivates estrogens, did so, only in the presence of an effective nutritional state, obtained by the administration of vitamin B Complex; in the absence of vitamin B Complex the liver no longer performed this function. Pathological uterine bleeding and subinvolution of the uterus following labor responded well to treatment with vitamin B Complex. The author believes that diabetes mellitus represents, in large part not insulin deficiency but impaired hepatic response to endogenous insulin, and this response may be greatly enhanced by nutritional treatment. Liver is itself the best source of whole B-Complex. Dessicated liver, in large doses, is most effective in providing the as yet unidentified factors essential to nutrition. The diet must also contain adequate protein. The B factors are not present in sufficient amounts in refined liver extracts such as those used in the treatment of pernicious anemia.

Editorial

CLINICAL RESEARCH

It appears that, from now henceforth, the laboratory must be the hand-maiden of the clinic, if valuable medical discoveries are to be made, since the perspicacity of the past generations of physicians has exhausted whatever store of findings reside strictly within the grasp of the pure clinician. The study of signs and symptoms alone seems to have reached a point where very little of importance can be added. Probably there are new diseases to be described though most of them would represent subdivisions of diseases already recognized. Thus there may be several kinds of Addisonian pernicious anemia, a minority group being one in which free hydrochloric acid is present in the gastric secretions. Again, the variation of strains of micro-organisms resulting from time and animal passage might conceivably produce clinical entities different from those now known to be produced by the same germs. Even in these two possible instances the chemist and the bacteriologist would perform essential roles in making the distinctions.

Thirty years ago there was confidence that competent clinical observation and long follow-ups of individual cases might throw considerable light on the manner in which chronic diseases developed. It is possible that in the mental field such methods may still be productive of very valuable knowledge, but in the general field of somatic disease, the experience of three decades has not been encouraging to the purely clinical investigator concerned with physical signs and symptoms. However, a *conception* is sometimes developed by a clinician which may have wide-spread influence in practice. One of the best examples of this is Alvarez' conception of "insanity equivalents" which has exerted a very important influence on other clinicians.

Psychosomatic medicine represents a new intensity on a very old note. The work of Dunbar, particularly, is sufficiently incisive to lend this phase of medicine, and this way of thinking about disease, a promising future. The astute physician of the past knew his *patient* as well as his disease, but Dunbar and other investigators of the psychosomatic persuasion have gone much further and have almost reached the point where the patient may be known from the disease he bears.

In gastro-enterology there are hundreds of problems to be solved but it is doubtful if any of them can be settled on a purely clinical basis. Biochemistry and physics are leading the way and at any moment are likely to make discoveries which, when converted to medical use, will open up new channels of approach. Psychology still is young and has not, as yet, given gastro-enterology all the invigoration of which it is capable. Nutrition, probably the most important phase of medicine today, is in its infancy and will, within the next few decades, exert a profound effect on gastroenterology as well as general medicine.

Book Reviews

TECHNIQUES OF HISTO- AND CYTOCHEMISTRY
By David Glick, Ph.D., 531 pages, $8.00. Interscience Publishers, Inc., New York, 1949.

This is a manual of morphological and quantitative micromethods for inorganic, organic and enzyme constituents in biological materials. Formerly chemists had no choice but to examine biological material in the test-tube, but now life is being examined in the cell where it belongs. To histology and cytology, the new techniques are applying chemistry and in the future we shall recognize cyto-physiology, which will give us direct information as to how a cell keeps alive and performs its somatic and species function. The book, strictly speaking, is highly technical and yet its theoretical value is appealing to any physician who is interested in the closest approaches which thus far have been made to the actual sources of vitality. As Prof. Bensley states in his valuable foreword, our chief hope of progress in the solution of the mystery of life rests in the very methods which this book describes.

DR. BASSLER COMPLETES FIFTY YEARS OF PRACTICE



ANTHONY BASSLER, M.D., F.A.C.P., LL.D.

We are happy to report that the testimonial dinner given Dr. Anthony Bassler on May 1st was a great success. It was held in the Grand Ballroom of the Hotel Commodore, New York City, and was held for the purpose of honoring him on the occasion of his fifty years in the practice of medicine.

Harry Hirshfield acted as toastmaster and speakers included Msgr. John Curry, Head of the Catholic hospitals of New York City, Rev. Walsh, Professor of Psychology at Fordham University, Dr. William Morrison, President of the National Gastroenterological Association, Dr. Martin E. Rehfuss, Professor of Medicine at Jefferson Medical College, Hon. Ferdinand Pecora and Hon. Peter Schauck, Judges of the Supreme Court, Dr. Foster Kennedy, Professor of Neurology at Cornell University Medical School, and Dr. Elihu Katz of the New York Polyclinic. The invocation was made by Rev. John Graham. This was accompanied by a musical program of prominent opera and stage artists. Dr. Bassler was presented with a book of letters and a gold medal.

Everyone is well acquainted with Dr. Bassler's clinical and academic record. He is the author of a half-dozen text books, dealing chiefly with digestive diseases and has published more than 300 monographs on abdominal conditions. He was the first chairman of the section on Gastroenterology and Proctology of the American Medical Association. He is past president of the New York Gastroenterological Association which he organized. He is also past President of the National Gastroenterological Association, an important organization into which he has put a great deal of effort.

While Dr. Bassler and American Gastroenterology grew up together, the expansion of the latter depended considerably upon the stimulus given to it by this physician, and possibly no one knows the history of American Gastroenterology quite as intimately as Dr. Bassler. On the personal side, he is a very human person, unselfish and blessed with a cheerful personality and with many wide interests which extend beyond the field of medicine. In his lapel he wears the ribbon of the Legion of Honor of France. This year he is president of the American Physicians Art Association, and is personally gifted with the brush. We hope, if he ever gets time, that he will write an exhaustive history of gastroenterology, for this would prove a valuable archive and a crowning effort of his long and fruitful career.

General Abstracts Of Current Literature

ABSTRACT EDITOR — M. H. F. FRIEDMAN

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EXPERIMENTAL MEDICINE

SECRETION

WOOD, D. R.: *Caffeine and gastric secretion.* (Brit. Med. J., Aug. 7, 1948, 283-285).

Using cats, it was found that caffeine injected intravenously in a dose which does not usually stimulate gastric secretion in the anesthetized subject, consistently potentiates the gastric stimulant action of histamine. A similar but less consistent effect was observed after theobromine and after theophylline. Possibly in human cases of ulcer or hypersecretion without ulcer, foods containing theobromine and theophyllin and drink containing caffeine ought to be limited.

MOTILITY

BROOKS, FRANKLIN P., STEVENS, LLOYD W., PENDERGRASS, EUGENE P., AND BASSOLS, FRANCISCO: *Experimental studies on the motility of the gastric mucosa in dogs. Preliminary report.* (Am. J. Roentgen & Rad. Th. 59, 4, 482. April, 1948).

The anatomy and physiology of the gastric mucosa has been reviewed with particular reference to the muscularis mucosa and its ability to produce movements of the gastric mucosal folds. Serial roentgenograms of dogs' stomachs, made after marking the curvatures with lead shot and the muscularis mucosae with thorotrast in the submucosa, have been presented to show movements of the mucosal folds, while the shot, representing the muscularis propria, remain relatively fixed in position. Similar roentgenograms made after the subcutaneous injection of mecholyl show movement of both the muscularis propria and the mucosal folds. The gastric mucosa is capable of movement due to contraction of the muscularis mucosae independently of the muscularis propria.

Franz J. Lust

PHYSIOLOGY

HARTIALA, K. AND KARVONEN, M.: *Anoxia and its influence on gastric secretion.* (Acta Physiol. Scand., v. 11, p. 85, 1946).

Three healthy male subjects were studied with reference to their gastric secretory response at high altitudes Alkalosis was prevented by prior administration of ammonium chloride. The test stimulus was histamine. Simulated altitudes were obtained by means of low-pressure chamber. With increase in altitudes there was a decrease in the response to histamine. Since the alkalosis of hyperventilation was prevented, the conclusion was drawn that the effect was due exclusively to anoxia.

PATHOLOGY

POPPER, H. L. AND NECHELES, H.: *Transition of pancreatic edema into pancreatic necrosis* (Proc. Central Soc. Clin. Res., v. 20, p. 65, Nov, 1947).

In the presence of edema of the pancreas the temporary clamping of the upper pancreatic artery results in the progression of the edema to necrosis. The authors believe that spasm of the arteries play a role in the development of pancreatitis.

TANTURI, C. A., LONCHARDI, J. A. AND BARFI, R. F.: *Protective action of sulfonilamide on experimental chloroform hepatitis.* (Surg. Gynecol. Obstet., v. 84, p. 477, 1947).

For a period of five days prior to anesthesia with chloroform dogs were given daily doses of 150 milligrams sulfonilamide per kilogram body weight. Anesthesia with chloroform for one hour was the hepatoxic agent. Usually such anesthesia results in a certain measure of liver damage. In the sulfonilamide pretreated animals the incidence and severity of hepatitis was less. Administration of the sulfonilamide during anesthesia was ineffective in protecting against liver damage.

HAMMER, J. M., HILL, E. J. AND SALTZSTEIN, H. C.: *Time relationship of complications encountered in 200 Mann-Williamson operations.* (Harper Hosp. Bull., July-August, 1948, Vol. 6, No. 4, 99-103).

The operation which is standard for producing experimental ulcers, consists of a gastrojejunostomy and an internal duodenal fistula with the duodenum anastomosed to the terminal ileum 12 inches proximal to the cecum. Complications following the operation fall into a pattern that may be used as a yardstick for predicting their occurrence and instituting measures for their proper management. Peritonitis, the greatest cause of death, occurs within the first week. Pneumonia, less common, may occur any time in the first month. Ulcer develops in the second week and continues, with cachexia, until death in about 9 or 10 months. Atelectasis occurs in the first week. Distemper occurs in the first two weeks.

SURGERY

ISGREEN, J., STONE, C. S. AND BAKER, J. W.: *Report on surgery of the stomach and duodenum for the year 1947.* (Bull. Mason Clin., June, 1948, Vol. II, No. 2, 43-49).

94 cases were operated on, 66 because of peptic ulcer,

2 for leiomyoma of stomach and 26 for cancer of the stomach. Most of the ulcer cases came to operation after 40 years of age. There were 44 duodenal and only 5 gastric ulcers. The authors believe that patients who suffer massive hemorrhage from peptic ulcer and who are 50 years old or older should be at once subjected to operation provided they can be seen, prepared and operated on within 24 to 48 hours after the onset of bleeding. When vagotomy was done in conjunction with gastric resection, results were good. Vagotomy also gave good results in 2 cases of simple uncomplicated ulcer. In one case of intractable ulcer vagotomy as the sole method of attack gave good results but in another it gave poor results. Vagotomy worked well in 4 out of 5 cases of jejunal ulcer complicating previous gastro-enterostomy. Six deaths occurred in the group of 26 cases of cancer of the stomach.

CALVY, G. L.: *Appendicitis and upper respiratory infections: a report of 18 cases at sea.* (Ann. Int. Med., May, 1948. Vol. 28, No. 5, 998-1002).

Among the ship's company on a naval escort carrier in the South Western Pacific, there were three "outbreaks" of appendicitis, numbering in patients respectively five, four and six, each outbreak associated with an outbreak of upper respiratory infection of virus type. The abdominal syndrome was clinically indistinguishable from acute appendicitis. The experience suggests that there may be a close relation between an epidemic type of respiratory infection and the onset of acute appendicitis. Twelve of the cases were operated on, and all the appendices removed showed some evidence of acute inflammation. Pain was the chief complaint. There was localized tenderness and muscle-guarding over the site of the appendix. Leukocytosis was seldom present.

BAKER, J. W.: *Problems involved in pancreatoduodenal resection.* (Surg., Obst. & Gyn., Jan., 1948, Vol. 56, 1-11).

The article deals largely with refinement of surgical technique but interesting physiological observations are offered. The entire duodenum may be removed in man without causing death. The removal of 80 percent of the pancreas causes no defect in either carbohydrate or fat metabolism, nor in the ingestion or absorption of food-stuffs, provided that the pancreatic remnant remains in connection with the upper intestine. In dogs, if 95 percent of the pancreas be removed and the remnant be left attached to the duct, a diabetes is produced which is more severe than after complete pancreatectomy. In the latter case hypolipemia develops and lipocaic is almost always needed.

JUDD, E. S., JR.: *Resection for lesions of the right portion of the colon.* (Proc. Staff. Meet., Mayo Clinic, May 12, 1948. Vol. 23, No. 10. 225-229).

Among the benign lesions requiring removal of the right portion of the colon (usually along with the terminal ileum) are terminal ileitis, non-specific ileocolitis, and occasionally tuberculosis. Cures result, but "skip areas" are responsible for many recurrences. In cancer of the colon, blood transfusions, antibiotics, the sulfonamides, high protein diet, amino-acid solutions, and streptomycin have combined to raise the resectability rate from 67 percent to 77 percent. The one stage operation is the one of choice and multiple-stage operations are a thing of the past. The hospital mortality has been lowered from 23.5 percent to 3.1 percent. In a series of 302 patients dismissed to their homes in the years 1907-1938, a follow-up shows 57 percent five year survival rate and 25 of the patients still were alive after 20 years. The new series of cases done in the past decade probably will show a still greater survival rate.

MCNEER, GEORGE T., GORDON AND BOOHER PACK, ROBERT J.: *Principles governing total gastrectomy.* (Arch. Surg. Vol. 55, 457-485, Oct., 1947).

A series of forty-one gastrectomies is presented, forty of which were done by the abdominal route. There were 13 operative deaths, a mortality rate of 31.7%. Seventeen patients survived an average of eighteen months, eight of these without nodal involvement at the time of operation averaged twenty-six months.

There are eleven patients surviving total gastrectomy: seven operated on for cancer are living and well, although three were operated on less than three months ago, and three operated for benign lesions have survived from six months to three years and four months. Five of 37 patients who had total gastrectomy for cancer of the stomach survived or are living over three years, an average of 13.6%. Total ablation of the stomach has been attended by surprisingly little alteration in nutrition.

A 13.6% three years survival rate for extensive cancer of the stomach marks progress in the treatment of a disease too generally considered hopeless.

Franz J. Lust

BRYNJULFSEN, B. C.: *Epidemic myalgia simulating surgical disease.* (Nordisk Med., April 23, 1948. Vol. 38, No. 17, 838-839).

The symptoms of epidemic myalgia are reviewed and attention is drawn to the fact that the disease may manifest itself through abdominal symptoms so pronounced that a patient may be referred for surgery. A case is described in which the abdomen was explored on suspicion of perforating ulcer.

WOLLAEGER, E. E., COMFORT, M. W., CLAGETT, O. T. AND OSTERBERG, A. E.: *Functional efficiency of the gastro-intestinal tract following resection of the head of the pancreas.* (Proc. Staff Meet. Mayo Clin., May 12. 1948. Vol. 23, No. 10, 245-247).

Intake-excretion studies were made on 10 patients on whom an operation for resection of the pancreas had been done, in order to assess the impairment of digestive and absorptive functions of the gastro-intestinal tract. A control series of normal persons was also carried out. The test diet employed contained 102 gms. of fat and 118 gms. of protein per day. In 3 patients

the ducts of the remaining portion of the pancreas had been ligated, thus preventing any flow of pancreatic juice into the intestinal tract. These subjects lost in the feces 60 percent of the fat and 40 percent of the protein ingested daily. In 6 subjects, anastomosis between the cut end of the remaining portion of the pancreas and the jejunum had been performed. In these subjects the losses in fat and protein varied from values equal to the other 3, to values only slightly above normal. Since this procedure is sometimes of value, it should be carried out. The oral administration of pancreatin (5 grams three times daily with meals) in persons who had had resection of the head of the pancreas reduced fat and protein losses by 50 percent. Patients, following this operation, should limit their fat intake to between 50 and 75 gms. a day, and should use about 130 gms. of protein and large amounts of carbohydrate to bring the total calories up to 3,000 or more per day.

Discussion on vagal resection for peptic ulcer. (Proc. Roy. Soc. Med., Sept., 1948, Vol. XLI, No. 9, 639-652).

The English attitude toward vagotomy for ulcer may be gleaned from a discussion in which several prominent surgeons and physicians participated. Vagal resection alone has given patients a tremendous amount of relief from pain, has lowered gastric acidity and contributed to the healing of ulcers. "The follow-up statistics present a more gloomy picture than the faces of the patients who attend the follow-up clinic." Gastric retention, diarrhea, dysphagia, weakness and dizziness constitute the chief late, post-operative complications. The resection must be complete, and the post-operative regimen must be strict. Further scientific study of operated cases is necessary to give a clear view of the significance of the complications. The trans-abdominal approach is to be preferred because it permits examination of the lesion. One of the discussants felt that vagotomy has no place in the treatment of gastric ulcer and that, even in duodenal ulcers, it alone canot be expected to cure large, old, calloused ulcers. One discussant, a physician, feels that a moratorium for vagotomy should be imposed for five years. "A procedure which is fraught with grave operative risks and is based on the erroneous interpretation of observed facts, which abolishes the nervous control of the gut and its sphincters and completely disorganizes its natural reactions and which, in addition, interferes with the normal responses of the gall bladder, pancreas and kidneys, cannot claim the support of physiological principles in justification of a surgical experiment on the human."

MCNEALY, R. W. AND SMITH, D.: *Unnecessary rectal operations done in the presence of cancer of the large bowel.* (Illinois M. J., Nov. 1948, Vol. 94, No. 5, 315-316).

This article is actually a plea for a complete scrutiny of the colon before rectal operations are undertaken Cancer of the colon, and indeed cancer of the rectum, may be present in patients who are unwittingly subjected to hemorrhoidectomies. In a series of 56 cases in which the rectal cancer could be felt with the index finger, 42.8 percent were subjected to unnecssary surgery. The trouble is, that, in such cases, malignancy is not suspected.

RECIO, P.: *Errors in the diagnosis of acute appendicitis.* (Acta Medica Philippina, July-Sept. 1948, Vol. V., No. 1, 43-54).

Perhaps there is nothing new that can be said about appendicitis, since it has all been said so many times, but it is instructive to read a skillful, illustrated, article on the diagnosis, and to find the following remark—"The more experienced the surgeon, the more difficulties he finds in making a positive diagnosis of acute appendicitis, aware as he is of the numerous pitfalls that lie in wait for the unwary.'

MISCELLANEOUS

RICHTER, C. P. AND HALL, C. E.: *Comparison of intestinal lengths and Peyer's patches in wild and domestic Norway and wild Alexandrine rats.* (Proceed. Soc. Exp. Biol. Med., v. 66, p. 561, Dec. 1947).

The problem was undertaken primarily to determine whether the wild Alexandrine rat is normally more herbivorous in dietary matters than the Norway rat. The Norway rats, both wild and domestic, were found to have a longer small intestine than the Alexandrine rat but the large intestine of the latter was larger than in the Norway rat. In both wild and domestic Norway rats the Peyer's patches are distributed regularly throughout the entire intestine but in the Alexandrine rat the patches are found in greatest numbers at both ends of the intestine. Peyer's patches in rats first become visible at 15 days of age and their number remain unchanged with age.

GRIMSON, K. S.: *Observations on abdominal visceral pain pathways in patients undergoing celiac ganglionectomy and vagotomy or sympathectomy.* (Am. J. Med., v. 3, p. 508, Oct. 1947).

Celiac ganglionectomy alone, celiac ganglionectomy combined with vagotomy, and right splanchnicectomy were performed on patients for various reasons. The conclusion was that a major portion of the pain pathways from the viscera go in the splanchnics by way of the celiac ganglion. Visceral afferent pain pathways were not found to be carried in the vagus nerves.

BRENNER, A. J.: *Scleroderma with gastrointestinal involvement.* (Rev. Gastroent., Dec. 1947, Vol. 14, No. 12, 869-872).

A case of progressive scleroderma is described in which, in addition to the dermal manifestations affecting the face, neck and extremities, the patient developed acute gastro-intestinal symptoms with abdominal pain and vomiting. Roentgenologic studies showed delayed passage of barium through the small intestine. The obstruction-like acute symptoms disappeared on the use of prostigmine. At present dihydrotachysterol (antitetanus factor No. 10) recently described by Bernstein and Goldberger (J.A.M.A., 130: 570, 1946) is being tried out.

STRINGER, P.: *Atelectasis after partial gastrectomy.* (Lancet, Vol. 252, Page 298, 1947)

Radiographic chest studies were carried out at intervals after operation in 55 patients subjected to partial gastrectomy. Lobar partial or total atelectasis were shown by 13 patients and other abnormalities were shown by an additional 13 patients. The immediate postoperative films were negative; atelectasis was revealed only after 4 to 24 hours after operation. Bronchitis, occlusion, bronchial pneumonia and other abnormalities were also shown. The 24 hour film is a valuable means of determining the occurrence of atelectasis bronchoscopy should be considered if warranted by the details of the roentgenogram.

ARZT, P. K.: *Psychosomatic medicine in general practice.* (Journal-Lancet, Nov. 1948, Vol. 68, No. 11, 423-427

This is a sound article in which the author exhibits a lack of prejudice. He believes that correct diagnosis can only be made by complete studies of the sick individual, and that a neurosis cannot be detected unless the physician completely understands the individual and his complex reactions.

REYNELL, P. C.: *Skin tests forsensitivity to liver.* (Brit. Med. J., Oct. 30, 1948, p. 784

From a review of the literature and personal experiments, the author indicates that almost all normal persons respond with a typical "weal and flare" to the intradermal injection of undiluted liver extract. It should not be concluded that a patient is sensitive to liver unless such a reaction is obtained with a dilution of purified extract of at least 1 in 100.

SELYE, H.: *The general adaptation syndrome and the diseases of adaptation.* (Nordisk Med., Oct. 22, 1948, 1913-1924).

The author gives a description of his own "general-adaptation-syndrome" which represents the reaction of the body to long continued strain of non-specific character, and is considered to have 3 phases. - the alarm reaction, the stage of resistance, and the stage of exhaustion. Boby-wide catabolism, and stimulation of the production of adrenal cortico-steroids are two of the chief mechanisms involved. Selye thinks that the following diseases may be illustrations of his syndrome. - some forms of hypertension. nephrosclerosis. Cushing's disease. Simmond's disease and Addison's disease, as well as others.

HAIN, E.: *On the occurrence of Cl. Welchii, Type F in normal stools.* (Brit. Med. J., Feb. 12, 1949, 271).

The author examined 108 stool specimens derived from persons in Hamburg, not suffering from enteritis necroticans and it was found that about one-sixth of these normal persons carried Cl. welchii type F in their stools. The strains recovered were, however, much less pathogenic for animals than those isolated from cases of enteritis necroticans, and further research is needed before it is possible to show that carriers are of any importance in the epidemiology of enteritis necroticans.

GILBERT, N. C.: *Acquired hiatus hernia.* (Miss. Valley Med. J., May 1948, Vol. 70, No.3, 85-87).

Hiatus hernia is almost always acquired, after the age of 40, the commonest cause being pulsion from below due to adiposity or pregnancy, but it may be due to traction from above where the long fibres of the esophagus are stimulated to contract reflexly from a gallbladder, gastric or peritoneal lesion. The symptoms may arise from the heart as an angina due to viscero-visceral reflex from the incarcerated stomach in which case decreased coronary blood flow actually is present at the time of the painful attack. Or, a non-productive cough may be the only symptom. Sometimes no symptoms are present at all. Diagnosis requires examination and perhaps re-examination by x-ray since the condition may not always be present at the moment of examination. The reduction of obesity, cure of visceral irritations and use of anti-spasmodics form the basis of medical treatment. *Paroxysmal auricular fibrillation* may be due to hiatus hernia. Many cases have long been treated as *angina pectoris.* The possibility of a hiatus hernia should be kept in mind at all times .

BAILEY, A. H. AND GUTHRIE, A. M. C.: *The examination of the gastric contents for tubercle bacilli.* (Med J. Australia, Nov. 8, 1947, Vol. II, 34th year, No. 19, 572-573).

All of the fasting gastric juice was removed before breakfast, neutralized if acid, incubated 45 minutes, then neutralized. If the juice was alkaline the procedure was carried out the other way around. High speed centrifugation at 3000 r.p.m. for 10 minutes gave the best results. Both smears and cultures were made. Jensen's modification of Lowenstein's media was used, using only non-fertile eggs not older than 3 days. Of 82 patients tested, 25 were found to show tubercle bacilli both by smear and culture; 21 gave negative smears but positive cultures. Cases showing roentgenological evidence of activity gave the most positive bacteriological findings. In the "less active" cases, bacteriological evidence was found only on culture. Perhaps cultural methods, correctly carried out, are as valuable as guinea pig inoculation.

WYMAN, A. L.: *Endogenous gas gangrene complicating carcinoma of the colon.* (Brit. Med. J., Feb. 12, 1949, 266-267).

The author describes a case with cancer of the colon presenting as a gas gangrene infection of the left thigh. The infection by Clostridium welchii had spread from the intestine to the psoas muscle by means of a tract connecting the carcinoma to the psoas sheath. He also quotes similar examples of gas gangrene resulting from diseases of the bowels, from the literature.

The Etiology and Treatment of Chronic Ulcerative Colitis (Non-Specific)

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The voluminous writings on non-specific ulcerative colitis (for which a better term would be colitis gravis) in the past twenty odd years attest to a greater interest in this disorder since Wicks described it in 1875[1]. In the fifty years before numerous etiologies for it were advanced, the activity mainly was touched off by Bargen in 1924[2] when he advanced the streptodiplococcus as the specific cause of the disease.

It is a disorder affecting principally young people in the formative and creative years of life, and often those with intelligence above the average. It runs a long course with a pronounced tendency to relapse, and despite much patient investigation, and accumulation of knowledge of various aspects of the illness, it still remains obscure in its etiology, uncertain in its course, and fickle in its response to treatment.

As to the etiologies and the suggestions of treatment that have been advanced in later years, the following are the more important and are presented with certain thoughts and deductions of the writer.

INFECTIOUS. Much interest has been attached to the diplococcus or diplostreptococcus of Bargen[2] and Bargen and Logan[3] to which may be added the diplococcus used by Cook[4] in his dental dog experiments. This organism was described by Soor many years ago as the diplococcus intestinalis and also by Conradi. It is not a highly virulent pathogen but, like many other intestinal organisms, in certain symbiotic combinations, can become parasitic or be important as a secondary invader, but it is not the cause of ulcerative colitis. At times it has been used with apparent success as a vaccine (serum) but in a specific way it is not to de depended upon. What has been presented concerning this organism is not biologically much different than any of the usual forms of streptococci met with in the bowel of which most forms met with are the more common types of streptococci. What is interesting about streptococci is that in the most serious cases of ulcerative colitis, a streptococcus may be the only organism present in the bowel.

Paulson[5] produced lesions of the colon with B. coli given parentally and Bassler[6] described a highly toxic hemolytic B. coli as important in the disease. While Hurst, Felsen, Bargen, and Dack have reported the importance of infectious agents in ulcerative colitis the first article on it occurred in 1913 by Bassler in which the coli organisms especially the high hemolytic types were given significance in the production of the disease.

The B. coli are found in the intestines of all mammals. Of the many forms, using Dunham's classification, no one form can be proven to be definitely infective. Yet the high hemolytic character of the B. coli found in ulcerative colitis, as compared to normal or other intestinal states, gives this organism a significance. In the microscopic pathology found in simple chronic toxic gut states the coli hemolyticus is an important etiologic factor when associated with other organisms especially those of the anerobic group. One must keep in mind that the coliform organisms are a large and varied group, there being sixteen different biologic strains of B. coli alone, and 26 more of the Escherichia genus classification. They represent a family of cousins from the innocent B. coli on one end to the highly pathogenic B. typhosus and B. dysentericus on the other. Thus they run from innocence to high pathogenicities and of all the intestinal organisms they are easily transmutable, one into another strain and virulence, according to how they are influenced by the symbiotic bacteriology and chemistry of the bowel. They must be considered as important in preparing the bowel for subsequent tissue breakdown by a secondary infection bringing on degeneration of the mucosal tissues. With other organisms in the mixed infection their action is lytic, and by constant reinfection of the mucosa from the lymph structures in and surrounding the gut, a vicious circle is brought about. It is this affinity for the lymphatic structures (the solitary glands in the mucosa, the pericolonic glands immediately outside and the mesentery glands) that is the cause of the recurrences which is the way the disease advances. A high hemolytic B. Coli associated with the secondary (mixed) infection of any of the pathogenic streptococci makes a vicious infective combination in this disease.

The B. dysenteria (paradysentery[7,8]) has occasioned much interest as a cause of ulcerative colitis especially since Felsen's work claiming that ten per cent of cases of acute bacillary dysentery result in a condition simulating chronic ulcerative colitis. What has been stated above in connection with B coli holds true with this organism which is one of the coliform family. If Felsen's point of view is taken, one would expect that these organisms would be recovered in all cases of chronic ulcerative colitis or at least in those who have a past history of an acute dysentery. This is seldom observed. However, it should be searched for, because if found, the results

is no reason to maintain they are important in cause and effect. Who has the method and ability to judge degrees of mental adjustments? Who has the method and ability to judge if, how, and why the colon is picked as the battle ground, or why the stomach, the heart, or the kidneys? As Ginsberg and Ivy[20] state, "If these emotional factors are etiologically concerned in the three diseases, why do they affect the stomach in some persons, cause mucus colitis in others, and in still others, as some believe, cause ulcerative colitis?" The writer believes that emotional states occupy about the same significance as allergic factors, namely to unstabilize an already diseased and degenerated colon.

An excess of lysozyme is supposed to dry the gut and make it susceptible to infection. In many of the chronic biotoxic intestinal states (putrefactious), the mucosa is atrophic and as dry as the back of the hand, yet there is no tendency to the disease.

Different workers have made much of chronic ulcerative colitis being a disease of pleomorphous etiological factors. Along the lines soon to be described its development is simple to understand. The error has been that the colon is easily unstabilized for many reasons, and that when any of these factors bring on symptoms too high a degree of etiological significance is given to them. They disturb the colon physiology, are functional in nature, and are not etiologic in the proper sense.

PHYSIOLOGY OF THE COLON. The history of colon disorders has been neither happy for the colon nor creditable to those who have exploited its misfortunes. A voluminous literature testifies to that common failure of trying to run before acquiring the more fundamental art of walking. One builds badly in the understanding and handling of a disease when the normal physiology of the organ in which it occurs is sparse, the known facts are few, and their interpretation difficult. Until we have a sound knowledge of normal physiology on which to build, disorder becomes a field for speculation, unhappily too often profitable, and progress must inevitably be slow.

In using the term "normal" pertaining to the colon one recognizes the wide scope of individual variation within the meaning of the term, variations that are not known or recognized, usually permitting the pathologic conditions of the colon to be overlooked or be designated as "normal". The recent history of the physiology of the colon has largely been advanced solely by the development of radiological technique and its application to the alimentary tract. Even the motor functions are still very incompletely understood and more knowledge is necessary on filling and emptying of the colon, haustration, mass movement, defecation and neuro-muscular control.

Nothing of much value is known of errors of secretion within the bowel and absorption from it. The no doubt important bacterial enzyme reduction of foods and possible toxic effects ensuing from them are still in the dark. The secretion and function of mucus and its association with the activity of muscle fibres, stimulus to nerve supply and phases of vascularity are mysteries to us. No attention is paid to the work of Florey[21] (1938) and Wolf and Wolff[22] (1942) plainly indicating the cleansing and protective action of mucus to the mucosa and its importance in preventing invasion from the dozens of pathogenic bacteria that inhabit the intestinal tract. The protective mucus here is contained in the invisible type (muco-protein)) that Glass has drawn attention to. He reasons logically that there is no separate substance called lysozyme. The importance of the acids formed from the fermentation of cellulose has some protective function but we do not know why or how. Lium and Porter, 1939, proved that when hyperemia, edema, hemorrhages or ulceration occurs, the goblet cells cease manufacturing mucus, the exhausted cell secreting a thin watery solution instead. As has been stated, the automaticity of the colon is more quickly disturbed than any other organ of the abdomen, and if, as modern psychiatrists believe, we think with the brain and all parts of the body, then the colon can be assailed in its function from both within and from anywhere in the body. We must then acknowledge that unless we have a reasonable degree of knowledge of the functions of the colon and how agents may disturb the physiology, we cannot understand its diseases.

MICROPATHOLOGY OF THE COLON.

Microscopic examination of what grossly appears to be a normal colon usually presents quite an array of minute pathologies. The literature is ample in teaching that in chronic constipation, simple forms of diarrhea, colon neurosis, spastic states, etc., we deal entirely with disturbed function without pathology, and yet it should be doubted in any prolonged so called functional disorders that a pathology in the walls of the colon is not present. This statement is based on the many instances at autopsy where colon disease was not believed to be present. In observations made years ago in the New York City morgue, the colons of fifty consecutive autopsies in instances where death was dramatically brought about, there were but nine instances of perfectly normal colons from a microscopic standpoint, and the examination of specimens since then in which disease of the colon was not suspected constantly proves the same. We all agree that the importance of a microscopic examination of tissue is essential for every proper pathologic report. Often an organ may appear normal enough on gross examination yet present minute structural changes.

These structural changes briefly may be presented as follows:

1. Detachment and lysis of cells of tubules. 2. Destruction of tubules. 3. Attached and adherent mucus. 4. Degenerated mucosa. 5. Submucosal edema. 6. Enlarged solitary follicles. 7. Interior cells of follicles broken down. 8. Thickened peritoneum. 9. Degenerated nerve cells. 10. Endothelial cells of blood vessels detached. 11. Blood vessels denuded of cells. 12. Hemorrhagic areas. 13. Sclerosed arterioles. 14. Thickened and sclerosed venules. 15. Phlebitis of venules 16. Cell detritis in submucosa. 17. Giant cells free in submucosa. 18. Free somatic cells. 19. Infiltration cells. 20. Fibrils of scar tissue. 21. Congestion (enlarged) blood vessels. 22. Large single and multinucleated cells. 23. Many lymphocytoid cells.

Unless what we have believed since Virchow's time of cellular pathology is to be scrapped, it is difficult to understand why minute pathology of the colon should continue to receive no attention.

BIOTOXIC INTESTINAL STATES

The baby is born with a sterile intestinal canal which presents swarms of bacteria a few days after birth. These are introduced from without. The only cause of digestive disturbances in infancy is dietetic, never bacterial. In a year or two the child has lost most of the immunities passed to it from the parents and has to build up its own from the pathogenic, zymogenic and saphrophytic organisms that are present in the digestive tract. For various reasons the so-called natural immunities against these organisms may not be acquired or acquired to high enough degree and a low grade biotoxic condition develops. The mucosa continuously subjected to this toxicity over years of time brings about the micropathologies described. The resistance to bacterial invasion and lytic agents then being lowered, bacterial infection assaults the mucosa with the production of congestion, inflammation and ulceration. When the colon is breaking down structurally it is not a question of this or that bacteria being present and a significance placed on some one as the cause of the disease. Any one of several bacteria is capable of producing it. What is important is the status of affairs in the first few decades of the individual's life before active inflammation and ulceration ensues, a part of medicine that is neglected. As I have reported 23 in 50 cases of well established ulcerative colitis the bacteriologies met with were:

Hemolytic streptococci specified types	42 cases
Green streptococci	21 cases
Nonhemolytic streptococci	17 cases
Alcaligenes fecaloides	33 cases
Staphylococcus albus	31 cases
Clostridium oedematis maligni	25 cases
Escherichia coli specified types	24 cases
Gram positive enterococcus	22 cases
Pseudomonas aeruginosa	19 cases
Erythrobacillus prodigiosus	18 cases
Clostridium welchii	7 cases

The product of decomposition in the intestinal tract of infants and normal children is remarkably small. In some, however, probably from the white staphlococcus, clostridium putrificus and Welchii changes take place in the coliform organism and the gut is distinctly toxic. The effects of this on the colon structures are not observed, but once established other contributing agents deepen the pathology. There may be some slight symptoms, like anemia, irritable mental states, retardation of growth, constipation, etc., but usually until about the middle of the second decade the individual is robust enough. The colon being an exceedingly sensitive organ is easily disturbed and no doubt changing from hour to hour. Being pathologic it is invaded and broken down. Here's where the significance of the hemolytic B. coli, various streptococci, streptobacillus, staphlococci and the coliform organisms come in. Mostly secondary invaders, they act as a mixed infection and break down the gut tissues, causing pericolonic gland and mesentery gland infection which then constantly reinfect the gut in a vicious circle.

In ulcerative colitis the sigmoid and upper rectum are infected first, and the process noted in this chronic sigmoiditis is a congestion accompanied with submucosal edema and hypertrophy of the mucosa. This goes on for months and years before true inflammation and ulceration due to bacterial invasion takes place. Thus the importance in diagnosing and treating sigmoiditis as a prophylaxis in preventing ulcerative colitis.

I believe that cases of ulcerative colitis start their development early in life by the sequence of, lack of building up the intestinal immunities required, a series of departures of normal physiology, a biotoxic gut state causing micropathologies in the colon mucosa, the effects of different agents in stabilizing the bowel, secondary bacterial infection, and reinfection from the lymph structures.

MATTERS PERTAINING TO CLASSIFICATION AND DIAGNOSIS.

The use of the term cure in connection with chronic ulcerative colitis cannot be used. Even after years of perfect health and normal appearing colon from an X-ray and proctologic standpoint, it still cannot be used because 39 of my cases in which there was every reason to believe were definitely cured after ten years broke out in recurrences (these late recurrences are always easy to control.) I agree with Kiefer[24] that the term control as good, fair and poor is all that is permissible. By good is meant where both the local and general constitutional

symptoms have been absent for at least five years, the patient being active and capable to stand strains, physical and emotional, eating any foods, no treatment, etc., without ill effect. By fair is meant that marked improvement had taken place, there is practically no disability, with but mild and easily controlled symptoms. Poor are those in whom continuation of symptoms has produced a severe degree of disability or complications.

In over five hundred cases treated the results of treatment were good in 69 per cent, in 28 per cent fair, and poor or operated upon in 8 per cent—this was on a two-year basis. All of these were severe cases of years standing. Even this eight per cent were a varying lot. Quite a few cases in which there was a poor status of affairs over considerably long periods of time without operation suddenly improved markedly, and there were a few who were classed good or fair that suddenly turned worse. There were so many instances of sudden change one way or the other that if a conclusion is reached one must still be open minded about it.

It also serves no purpose to classify the cases as left sided, right-sided or entire colon, or in duration of the disease or ages of the patients. Of interest here is that the younger the patient the more often the disease is serious and the older the patient the easier it is to control. Also, in the vast majority of the patients the disease begins in the lower left colon and when confined to this area ulcerative colitis is easier to control. The disease too, should be classified as primarily mucosal or lymphatic. The lymphatic cases are those in which the lymph structures are deeply involved early, are the most difficult to control, and comprise the larger number requiring surgery. The mucosal forms comprise those in which the lymphatic structures are less involved and supply the larger number for medical handling. These latter can often be diagnosed by small projections along the margin of the colon. If follicular cell breakdown and a low grade mucosal inflammation are present, pus, blood and leucocytes and macrophages may be met with in colon washings. My observations do not agree with Bercovitz that by this means one can with sufficient clinical accuracy make a distinction between "bowel dysfunction" and pathology especially in that of the degenerated toxic type. He states that no cells are shed from a normal colon, but cells are commonly shed in chronic toxic states without even simple congestion. Often no cells are found even though definite pathology exists, and in what ordinarily is designated as normal they may be found. If this could be depended upon this type of examination would be of interest to diagnose the potential ulcerative colitis case although even here more dependence must be placed on the history, X-ray films and proctologic appearance. Bowel scrapings, the chemistry, bacteriology and character of the feces are sometimes of interest when in doubt.

Under proper medical treatment the less severe cases certainly can be gotten in hand easily, practically every one of them. When the profession meets the responsibility of earlier and better diagnosis and treatment in chronic sigmotiditis the instance of severe disease and those requiring surgery will be very few indeed.

No case of chronic diarrhea should be judged as due to chronic ulcerative colitis until it has had a thorough examination especially for the other causes of diarrhea, and proof of colon or procto-sigmoid involvement is definite. Of those with continued diarrhea and pathology, about two-thirds will be due to chronic ulcerative colitis. As the cases are met with the entire colon will be involved in about half, and the rectum, sigmoid and descending colon in about one third. In about one-fifth the process stops at the hepatic flexure or is segmental. In those with short histories or very superficial and moderate involvement, the colon may appear almost normal and rugal studies for diagnosis are necessary. The diarrhea in left-sided cases may have existed for several years, the disease never having extended upward or taken on significant involvement of the lymphatic structures. It should not be taken as definite that those which show absence or minimal amount of change from the X-ray standpoint are the more favorable for treatment because some of the serious fulminating cases and some of the most prolonged show none or only slight anatomical changes from normal. Nor can the course of the disease be judged by X-ray alone. Often in a cured case that had shown definite change by X-ray, after years of time, the colon reconstructs itself enough for it to appear quite normal. In the majority of the cases some degree of the pathologic X-ray picture persists, and according to Ricketts, Kirsner and Palmer[25], regression occurs in approximately ten per cent.

In the past twenty years the writer has seen 542 cases of chronic ulcerative colitis, non-specific in classification. Of these 161 are left out of consideration for various reasons. The remaining 392 cases were under more or less continued observation and had been treated for a sufficient period to draw some deductions. During this twenty year period changes in treatment took place but these were not of such fundamental importance as to modify the figure very much. I desire to repeat one must keep in mind that the disease is so fickle, experience with the cases so variable, and the results from different items of treatment so unpredictable, the status of disease so difficult to classify, that, even more so than in peptic ulcer, statistics are only of relative value. There are differences in the types of cases and results from treatment in private as compared to those that were in hospital practice, the latter tending to be more poorly handled, more severe, the fulminating form, those with complications and those in which surgery is more necesssry. Only those under private observation are presented.

TREATMENT

It is well to begin treatment with the patient in bed which is an essential in the febrile and fulminating cases. The principle of rest brings about physiological reconstruction of depleted bodily functions and mental energies. In the average afebrile case in which the lesion is limited mostly to the left side they may be handled in an ambulatory way. It is well, however, in order to build up physical and moral tone, to save the patients from the possibility of emotional upsets, to symptomatically control any distressing symptoms, and treat any focal infective conditions, that the patient be hospitalized for a few weeks time. By continued rest and heat to the abdomen a moderate diminution of the hyperactivity of the colon occurs, somewhat limiting cramps and diarrhea and often doing away with opiates and sedatives. Bed treatment is possible in about one-half of the patients, yet in about one case in five the patient had already had a sojourn in bed and is reluctant to go there again. Limited financial means operated in about one-half. If a start in bed is not practical, it is well to cut out all social activities, house responsibilities, encourage resting, and have a happy and pleasant atmosphere around the patient.

This early stage of treatment is the best time to question the patient on any worries, fears and anxieties, emotional conflicts, maladjustments, etc., and exercise common sense, the teaching of the Bible or Talmud to straighten them out. If the job requires psychoanalytical treatments is is better not to conduct these when the patient is in bed. Atrophine and phenobarbital are often useful.

Often intravenous therapy is necessary to overcome dehydration, subnutrition and debility. Only blood and plasma are employed since all the others are only poor substitutes. Intravenous mercurochrome may be employed alternating with the blood and plasma. The diet and vaccines are started. At all times care must be taken that the patient not catch cold and if one is contracted it is best for him to remain in bed and treat it. A recurrence is easily brought about by a respiratory infection. There is an unrecongized law of mucous membranes operating through the sympathetics in which when one area is inflamed congestive reaction takes place in the others. In a person with an acute cold in the head the intestinal mucosa will be congested.

DIET. No restrictions of nutritious foods should be carried out in treating chronic ulcerative colitis. Two fundamental rules are important.

1. The taking of the largest amount of protein foods possible in order to meet the shortages of nutrition caused by the diarrhea, infection, weight loss, anemia, avitaminosis, etc., to which amino-acid and supplemental feedings are added, but milk is not allowed. Sometimes infusions containing amino acids are employed. Effort should be made to keep the serum protein at the highest possible level and to improve the anemia (usually two difficult things to accomplish early in the treatment), and by protein per os and low carbohydrates to stimulate the innocent and restrictive types of Gram negative (B. coli) organisms.

2. The physical character of all foods should be fluid or semi-fluid so as to digest the largest amount in the upper levels of the small intestine and so that one has the smallest amount of residue to collect in the colon. Solid foods should be comminuted, put through grinders, cut fine, etc. About twenty-five years ago when the writer advised high feeding in ulcerative colitis at an A.M.A. meeting no one agreed with it. Today it is pleasant that it is more generally accepted but it should be still more so.

ALLERGY. In the majority of cases of ulcerative colitis the history of an allergy to certain foods cannot be obtained. When it is, it should receive definite attention. Since milk often lights up a diarrhea in instances of bacillary dysentery a long time after the condition had subsided, it is not allowed. Since milk, eggs and wheat comprises about 90 per cent of the food allergies, these are eliminated at the start of treatment. Other foods sometimes of importance are shellfish, strawberries, cheese, nuts, pork and chocolate and these require watching. Since it is important to maintain as high a nutrition as possible, and skin tests to discern food allergies have usually been worthless, the important foods mentioned are allowed as soon as it looks feasible. So food allergies (like psychotherapeutics, rest, etc., and other measures) are important in keeping the colon more stabilized. In my experience, antiallergic diets that are difficult to follow (Rowe and Andresen) are rather unsatisfactory, especially in the ambulatory case . However, there is no objection to employing these eliminating types of diet because of the bland, low residue properties which, in my opinion, accounts for most of the good effects that have been attributed to them. With the exercise of a little interest for diversity the plan mentioned is easy to follow for long periods of time. As soon, however, as improvement is definite, eggs and wheat may be allowed.

VITAMINS. Moderately large sized doses were used by mouth and parental injections. Natural B. complex and injections of crude liver answer well. Following improvement one of several preparations in capsule form, containing large doses of vitamins with liver, ferrous iron and folic acid are given and these kept up for months. Effort should be made in the diet to employ foods high in vitamins, since natural vitamins are of more value than synthetic ones. Often the vitamins

from foods with iron by mouth and liver by injection were employed.

DIARRHEA. Measures may be used to control a large number of movements where these are too distressing. One of the opiate preparations is best used, occasionally, but, if possible, rest and sedatives should be tried first. During the course of treatment in all cases and for long periods of time, a teaspoonful of bismuth subgallate is given in water before breakfast, (sometimes also at bedtime) and this may slow down the movements. Occasionally intravenous alimentation maintained for several days puts a badly-irritated bowel at rest. In order of procedure then are I, bismuth subgallate, II, rest and heat, III, opiates, IV, Only fluid foods orally and intravenous medication for several days.

VACCINE. Vaccines, made of any of the coliform organisms have been most successful in my hands. Most of the Gram negative organisms when virulent are exogenous toxin producers and thus their vaccines have been successful. Every infection presupposes a lack of immunity. It is believed by some that the kicking up of an active immunity could just as well be brought about by any of the non-specific proteins used for the purpose, and that if a vaccine is beneficial, it is so only because of the protein in the bacterial body. An exogenous bacteria carries a specificity inherent to it. In several bacteria of the same genus there may be a slight similarity in the toxin.

It has been brought out that the intestinal bacteria are the infective factor and these are added to an already degenerated pathologic colonic mucosa. This infection, which is a symbiotic mixture of organisms, is what breaks down the tissues, mucosal and lymphatic. As has also been brought out, the organisms of greater significance here are those of the coliform types and that this group comprises forms all the way from the B. coli on one hand to the specific forms of B. dysenteriae, B. para-dysenteriae, B. typhosus, etc., on the other. While there are specificities between them in the production of different diseases it is impossible to assess this. The first vaccine used was the B. coli from the patient when this was highly hemolytic. If not highly hemolytic a strain from another source was employed. It was found that as good results could be obtained from a polyvalent B. dysentery vaccine of organisms taken from instances of acute and chronic dysentery. Sometimes the patient's hemolytic B. coli are added to the stock strains of the paradysenteriae in half and half quantities.

The use of vaccines for therapy may be criticized and for various reasons their use here may be depreciated, but after twenty years work with this disease, I am satisfied that often much benefit has come from their use although I am perfectly willing to admit I do not know how or why. The type of vaccine used was highly concentrated, the doses used never more than would give a local reaction larger than a twenty-five cent piece. I have used one of the three forms mentioned in all the cases I have handled especially the two types. The vaccine and sera recommended by Bargen were used in about twenty-five cases but I doubt the results are as good in a general way as with the forms mentioned. Drug instillations and irrigations, no matter what the drug, are useless and often vicious. You can not sterilize a colon with them any more than you can sterilize the ocean.

MERCUROCHROME. The intravenous use of mercurochrome was first described by Young and Hill[26]. In the next seven years a number of articles on its use in ulcerative colitis were published by Einhorn[27], Rosser[28], Smithies[29] and Rouse[30], reporting optimistic results. As time went on it proved to be a dangerous drug in the doses employed, many of the reactions being extremely severe. Some persons seem to exhibit an idiosyncracy to mercurochrome exhibiting rapid and considerable rise in temperature, gastric irritation, diarrhea and kidney dysfunction. At the request of the American Medical Association, the manufacturers were advised to discontinue supplying it for use by the intravenous route. Being a bacteriocide its use was originally suggested for systemic infections and it never was intended or recommended for intravenous use in chronic ulcerative colitis by its manufacturers. Consequently no investigative work was done to standardize the dose and estimate the safety of the drug. In 1927 in a case of streptococcus septicemia and one of brain abscess in which mercurochrome was used intravenously, the autopsies were interesting in that the interior of the colons were deeply stained and apparently the colon was an important source of its elimination. Other than the kidneys, the other tissues of the body were not stained.

Its early use in ulcerative colitis was to control the infection in the bowel wall. No means had yet become practical for accomplishing this, but what was of interest to me was its use to help control the reinfection factor that infects the mucosa from the glands and thus causes the recurrences. It must be recognized that chronic ulcerative colitis is an infectious disease that advances intermittently and each recurrence is a deeper establishment of the disease. If after injections every fourth day for four to six weeks definite benefit is not accomplished, mercurochrome should not be expected to be of any help. In the early days the dose of mercurochrome employed was approximately 0.168 grs for a person 50 kilos in weight. My minimum dose is 2 cc of a 1 per cent (0.02) solution and this raised in the absence of reaction to 5 cc (0.05 gm). In the vast majority of my cases mercurochrome intravenously was employed, alternating with 250 cc blood transfusions one each three or four days.

Some thousands of mercurochrome injections in from 2 to 5 cc quantities of 1 per cent solution have been given without a reaction or one untoward result. Many times when a recurrence from the disease occurred, a few doses of mercurochrome was all that was necessary to control it. I would advise against its use in those under 10 or over 50 years of age, or those with suspicion of kidney disease, and that the dose initially, never being larger than about one-third of that used years ago.

DRUGS. Practically none of my cases were treated with antiserum antidysenteric serum, or by sulfa drugs. Usually the patients had been taking sulfa drugs in various forms before I saw them. None of these drugs were curative to any dependable degree in the well established case even admitting that an occasional case would show some benefit with the non-absorbable forms for a short spell. In this one form of the non-absorbable sulpha drugs one is as good or as useless as another. It has been reported that after the oral administration of the non-soluble sulfa drugs there is a decrease of the gram negative and an increase in the gram positive organisms. This does not occur with assurance and it is a mistake to bank on it. In the very early stages of the disease in about two-thirds of the cases a limited benefit may take place, but as a rule I do not see the cases that early. In most of my cases, the disease has existed for months or years. A few cases were treated with the antibiotics, penicillin or streptomycin, neither of which, in my experience, are of value in this disease. With so many things that were used for the treatment in the years gone by each seemed to be of value all eventually being discarded for something new.

The idea of "wetting down the mucosa" with sodium alkyl or lauryl sulphate as a control of lysozyme and pancreatic secretions has been advanced. A few instances of benefit have been reported, and many more will have to be reported to judge the value. Since lysozyme is a secretion of the intestinal mucosa and is markedly enhanced in ulcerative colitis one may ask if the increase comes before and if it is important in producing the disease- or after the disease is established. In ten cases of atrophic colitis (colitis sica) the titre was about ten times that of normal and yet no ulcerative colitis occurred. In twenty-six cases of ulcerative type the lists of the pancreas (external secretion) were not above normal and one may question this as an etiology, as Portis suggests. Of interest in this connection is the increase of lysozyme with emotional upsets. In the vast majority of instances of emotional disturbances without ulcerative colitis (and peptic ulcer) no increase occurs and it will be found that in the majority of instances of ulcerative colitis (and ulcer) in the chronic state increase of lysozyme is not present or present to marked increases, still mucus stripping, whether as a cause or result, should have significance and further studies in this connection should be encouraged.

Mention should be made of bacteria protein injections (intravenous typhoid vaccines). A number of years ago intravenous typhoid was used in 30 consecutive cases. About half showed some improvement in the diarrhea but it was judged that the routine management they were receiving deserved the credit and also because of the shocks the treatment was discontinued. Many of the cases have an achylia or low acidity from a granular gastritis which the colonic infection brings about. One cc of diluted hydrochloric acid in four to eight cc of gastron well diluted and sipped after meals often is of benefit.

Also of interest was the routine early use of antiamebic therapy in cases in which ameba histolytica and cysts were not found on two examinations, one made for the trophozoites, and one for cysts. Since errors are inevitable in the examination for the parasite of amebiasis or a capable parasitologist not be available, there is no objection beginning the treatment with a run of the nontoxic antiamebic drugs (vioform, diodoquin). Their use surprisingly often brings about a rapid improvement in the diarrhea. This temporary benefit occurs in about a quarter of the instances of chronic ulcerative colitis. If amebiasis had been present or an infestation exists, the case should be treated as one of amebiasis and not chronic ulcerative colitis. In such cases it may eventually become evident that chronic ulcerative colitis occurred from a secondary bacterial infection which the amebiasis had brought about. The vast majority, however, are those of non-specific etiology.

ANEMIA. HYPOPROTEINEMIA. These were corrected by 250 cc blood transfusions given every third or fourth day and kept up for weeks. Even in the presence of only moderate anemia these transfusions were employed, because there are other constituents in blood than hemoglobin and proteins that are helpful. These are contained in the immunity producing bodies, which are especially helpful in these cases. Improvement allows the iron to be discontinued although sometimes it helps to constipate and may be continued for that purpose. The hypoproteinemia is benefitted by diet and intravenous amino acids.

PSYCHOTHERAPY. Since the writer believes that emotional disturbances are not fundamental in the production of ulcerative colitis psychiatric treatment is considered as non-important. The average physician should take an interest in the patient's problems, make correction and give advice so as to bring about adjustments. When the patient was well enough, a few questions were asked at various times on matters of personal faults, domestic, family or financial difficulties, etc. The importance of their connection "so that the body can become more nor-

mal" is pointed out and advice given. It should be emphasized to the patient that fear, anxiety, sudden excitement, love, hysteria, etc., brings on depression of mobility, secretion and absorption in the digestive tract.

SURGERY. Chronic ulcerative colitis is a medical disease and should be treated medically as long as there is any hope for improvement. It is slow in recovery and it must be remembered that it is a young person's disease (average 28 years). I once said at an A.M.A. meeting, "If you can keep these people living long enough, time will benefit and often cure the disease." There is no disease in medicine in which the patient can reach such a state of emaciation, debility and illness and yet recover. The decision for surgery carries much responsibility and should be made by an experienced person, not only a surgeon and never early as Leahy suggests. There also is no disease in which operative statistics vary so markedly. Considering mortality and the unhappiness of an ileostomy or cecostomy, one usually is influenced against operating upon these cases early. There are, however, certain criteria that serve as guides. These may be said to be,

I. Where the disease has existed for a length of time without substantial benefit, and general health is failing in spite of good medical handling in a conscientious patient. Cattrell[31] reports that about one-quarter of the cases at the Lahey Clinic are operated upon. This, to me, is a surprisingly high figure, and I question whether it is justified even though the mortality be less and early operation permits of a few more closures of the ileostomy. If the patient's general health and weight hold up pretty well and the invalidism is only moderate (controlled case) one is justified in continuing the medical handling. If cases are operated upon earlier with the usual surgery I believe that many would be operated upon unnecessarily. The acute fulminating and continued febrile case have to be included in this connection. II. Perforation, which occurs very infrequently. III. A long history of hemorrhaging from the bowel with continued diarrhea. IV. Internal and multiple external fistulae of the rectum. Here the fistula should not be operated upon until the disease is controlled because of the danger of sloughing. If the disease is still on, it is best to do an abdominal operation and leave the fistula for attention at some time afterward. V. Strictured state too high for manual divulsion. Those in the rectum usually can be controlled. VI. Malignant disease which occurs in one or two per cent of the cases even if colectomized and the rectum left in.

Recognizing there are exceptions, operation is not definitely advised in left sided lesions with moderately severe symptoms even if of some years standing, in remissions, in the very young and old, for anemia, debility, moderate loss of weight, for excessive and continued diarrhea, abdominal or rectal distress, for arthritis or polyposis even if the case is being controlled only moderately well. Obviously, the cases operated upon early show lower mortality figures from ileostomy and colectomy and a higher incidence of a final successful ileosigmoidostomy (10 per cent according to Cattrell) as compared to the surgeon who operates when the disease is more advanced (6 per cent - Cave). Cattrell[31] stated an ileostomy is not a cure, and it may be asked if the removal of an organ (colon) could ever be designated as a cure. Statistics of the course of patients in the years after ileostomy and colectomy are too few for clear vision. Considering the rate of mortality, the distress of carrying an ileostomy, and the low incidence of closing an ileostomy even under the best conditions should cause the surgeon to hesitate in this disease.

Carcinoma in chronic ulcerative colitis is reported by Lyon[32] as 1.9 per cent, Jackman, Bargen and Helmholz[33] an incidence of 6.3 per cent in 95 children, Bargen, Jackman and Kerr[34] 3.2 per cent in a group of 871 cases of all ages, Bockus[35] 1.5 per cent in 200 cases. Cattrell (Lahey Clinic) 7 per cent (personal communication). While carcinoma may develop from the inflammatory pseudopolyps of ulcerative colitis, in chronic ulcerative colitis it is rare. In my cases followed over ten years it occurred in two instances (1 per cent), an incidence of colon carcinoma, not distinctly beyond that seen in non-ulcerative conditions. Cattrell states that 1 in 3 who had ulcerative colitis nine years or more and were operated upon developed carcinoma. One is reminded here of McCarthy's figures some years back of carcinoma in gastric ulcer. Polyposis accompanying chronic ulcerative colitis is generally accepted as the designation of a bad case and one in which colectomy is advisable. There were many instances in which the symptoms have abated and the patient got along well even though the polyposis pesisted. Records on these were not kept, but they were numerous enough to modify the present day point of view that surgery is always indicated. These cases are a type of pseudopolyps secondary to inflammation, and, unlike true polyps (which have a non-inflammatory origin and are permanent) under continuation of proper treatment their presence has lost a great deal of their significance to me and today I am quite conservative about them. On the other hand, marked fistulae formation, suspicion of malignant engraftation, marked continued reduction of general health are signals for surgery . Not a few of the strictures in the rectum can be stretched either by finger or apparatus. Divulsion by surgical methods is most inadvisable unless the case has shown definite control of the disease.

The question of surgery should be left quite up to the personal equation of the individual. If the person is reasonably in control of the condition, able to be fairly active up and around, work, etc. I advise conser-

vatism. If the invalidism is definite and continues so in face of proper treatment or complications exist, mention of surgery should be made. There are people who would rather commit suicide than carry an ileostomy, and others who don't mind them at all. Some even are so satisfied that they will not agree to a reconstruction job making possible the elimination of the ileostomy bag. So the percentage of cases in which major surgery is recommended is variable. In my practice it is about 5 per cent, and usually performed for complications.

I here would like to present the use of appendicostomy (cecostomies) with irrigations. Appendicostomy has been discarded and it should be reestablished and be popular as an addition to the medical handling of chronic ulcerative colitis. As already stated, the use of enemas driving the infection higher into the right side is definitely a procedure of malpractice, no matter how skillfully done or what the solution used. An appendicostomy (cecostomy) is a very minor surgical operation and can do no harm if it does no good. It is not inconvenient to the patient and when properly performed has no drawbacks connected with it (such as leakage, closure, etc.) What I observe today in handling chronic ulcerative colitis is a poor effort at early diagnosis and medical treatment and then a jump to ileostomy, colectomy and perhaps removal of the rectum. What would be better is more assiduous medical attention, an appendicostomy if after a reasonable time improvement is not manifest, solely as a medical treatment for irrigations. On the whole appendicostomy (cecostomy) has been performed 32 times and only four required more serious surgery after that. The four irrigations used were usually normal saline solutions or weak solutions of mercurochrome or merthiolate, once or twice a day, kept up until the improvement is satisfactory. The injections are then reduced but the appendicostomy is kept open for several years. It does no harm and one should not be in a hurry to close it. Should further surgery be necessary the small appendicostomy opening would not interfere. The incidence of doing an eventual ileosigmoidostomy after the operation has not been as frequent as one would have hoped. Were the number of these cases higher, a more happy outlook for colectomy would prevail in this condition. After the ileostomy if colonic irrigations are introduced from the cecum (by way of appendicostomy or distal stoma of the ileostomy) the number of final ileosigmoidostomy would be increased.

At the A.M.A. meeting of 1947 two opposite points of view were expressed. Bargen was of the opinion that the condition should be judged as a medical one, operations not being in order, and Leahy stated that operations should be performed more often and earlier. My own point of view is that no general statement is important, and the only thing of value is the wisest judgment in the individual case. In the six months or more interval between the ileostomy and the colectomy the possibility of the lower left side being practicable for hook-up can only be predicated on the appearance of the colon by X-ray, and whether or not the mucosa of the rectum and sigmoid has improved sufficiently. Various other means of estimating this (examination of material that comes away from the colon for blood cells, pus, bacteria etc., the constitutional improvement of the patient, and the continued use of some type of colon instillations, tannic acid, mercurochrome, hydrosulphozed, etc), have produced very few successes. If a major operation is contemplated, it is worth while to have the patient see one or two individuals who have had it done so as to build up assurance.

I agree with Bargen and Paulson that intractability depends on the skill and perseverance of the medical advisor and the man managing the disease. When these are satisfactory, ulcerative colitis will be found to be a disease that is curable and controllable to a high percentage by medical means, and cases so handled will leave few cases for operation. As to prophylaxis the diagnosis and treatment of the common condition of chronic sigmoiditis in the young is most important.

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Sulfonamide and Antibiotic Therapy in Proctology

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The sulfonamides and antibiotics have radically revolutionized general medical and some surgical therapy. In many cases, however, their role has been unduly stressed. It will be the purpose of this paper to review briefly the sulfonamides and antibiotics available to the proctologist, and the indications for their use.

It would be well to discuss first the available sulfonamides and antibiotics in general before dealing with their applications in specific pathologies.

Of the sulfa drugs employed in proctology those that are poorly absorbed from the intestinal tract are probably the most commonly employed. These would include sulfaguanidine, sulfasuxidine and sulfathaladine. These drugs markedly reduce the bacterial flora in the large bowel. Inasmuch as they are poorly absorbed by the gastro-intestinal tract they rarely produce renal lesions. However, skin rashes and drug fever may occasionally result.

Sulfadiazine, sulfamerazine and sulfathiazole are also valuable to the proctologist. Sulfanilamide is less frequently employed.

A combination of sulfa drugs, such as sulfadiazine and sulfamerazine, has been introduced with the theory that a mixture would be less apt to produce renal damage or calculi. The bacteriostatic effect is considered to be additive while the possibility of renal damage is theoretically no greater than that for each drug of the combination alone. It is not yet possible to pass final judgment upon the value of combined therapy. However, the combination of sulfadiazine and sulfamerazine may be recommended.

Parenteral administration of sulfonamides is not usually required in proctology.

The antibiotics available to the proctologist include penicillin, tyrothricin and streptomycin. Of these penicillin will be the most frequently employed. Crystalline penicillin G may be prepared and administered in sterile distilled water or isotonic solution of sodium chloride. However, this preparation is required in twenty-five thousand unit dosage at intervals of three hours. Thus, frequent intramuscular punctures are necessary. To decrease the frequency of administration crystalline penicillin G has been prepared in three hundred thousand unit dosage in oil and beeswax. This preparation may be given intramuscularly once every twelve hours.

Procaine penicillin is a poorly soluble salt and is absorbed slowly, thus producing prolonged blood levels of the antibiotic .A single intramuscular injection may be given daily in a dosage of three-hundred thousand to six hundred thousand units. Procaine penicillin G has also been prepared for aqueous solution. A one cc. dose of this suspension contains three hundred thousand units of penicillin in chemical combination with approximately one hundred twenty-five milligrams of procaine base. A single intramuscular injection of three hundred thousand units produces therapeutically effective blood levels for twenty-four hours in most patients, and for thirty-six hours in approximately fifty percent of patients. In the aqueous preparation of procaine penicillin G there is the advantage of an absence of oil, wax or other foreign material.

Oral and inhalation penicillin therapy are not of particular significance to the proctologist. If it is desired to prescribe penicillin by the oral route crystalline penicillin G should be recommended in a dosage of one hundred and twenty-five thousand units at three hour intervals day and night.

Tyrothricin can only be employed as a topical antibiotic agent. I have already described its application in proctology.[1] Isotonic solutions containing 0.5 milligram of tyrothricin per cc. may be employed for irrigation or as a wet dressing. It is probably best to avoid combining tyrothricin with penicillin inasmuch as sensitivity to penicillin is easily produced by topical application. Indeed, the quickest method of producing a generalized penicillin sensitivity is by local treatment of open wounds with solutions, salves, creams, powders or pastes of penicillin.

Streptomycin should never be given in a concentration over three hundred milligrams per cc. It has a definite but limited value to the proctologist. The total dosage may be dissolved in one cc. of sterile distilled water or sterile isotonic sodium chloride solution, and should be administered intramuscularly. It must be remembered that streptomycin is directly toxic to the auditory and vestibular apparatus, perhaps proportional to the dose used. Thus, this antibiotic must be emtion. It is also worth noting that streptomycin therapy easily produces resistant bacterial strains or resistant mutants. However, such an occurrence is infrequent during sulfonamide or penicillin therapy.

TOXIC MANIFESTATIONS

The proctologist will only employ the sulfonamides or the antibiotics where the indication is direct and evident. Indiscriminate administration of these drugs may lead to sensitization or toxicity. As I have already mentioned in the matter of topical penicillin therapy, sensitization is most rapidly established when antibiotics or sulfonamides are employed locally. Thus, it is best to avoid such topical application unless absolutely necessary.

The nausea and vomiting of sulfonamide toxicity are of little consequence. It would seem that these toxic reactions result from an effect upon the central nervous system rather than from gastric irritation.

A relatively common reaction is drug fever. Such fever frequently follows sulfathiazole administration. Sulfadiazine and sulfamerazine are not often followed by drug fever.

Sulfonamide skin rashes are common. As with the sulfa fevers sulfathiazole is the most common offender and sulfamerazine and sulfadiazine are the least toxic. Photosensitization is important and these patients should be kept out of the direct rays of the sun. Fatal exfoliating or bulous dermatitis is rare.

Dizziness is not particularly common with sulfathiazole, sulfamerazine or sulfadiazine, the sulfa drugs most commonly employed by the proctologist. Cyanosis rarely follows the use of these drugs.

Similarly hemolytic types of anemia are rare when sulfathiazole, sulfadiazine or sulfamerazine are administered. Cyanosis and anemia are common, however, during sulfanilamide therapy.

Agranulocytosis is relatively frequent with sulfapyridine therapy, but rare during sulfathiazole, sulfamerazine or sulfadiazine administration. This blood change generally appears when treatment is continued beyond the twelfth day.

Hematuria, by contrast, occurs frequently during sulfathiazole, sulfamerazine or sulfadiazine therapy. Impairment of kidney function appears to be more common with sulfathiazole than with sulfamerazine or sulfadiazine.

Hepatitis is an uncommon reaction, as is stomatitis, peripheral neuritis, sulfa arthritis, and gastrointestinal bleeding.

The point of this discussion is merely to emphasize the possibility of toxic reactions and the need for close observation of patients who are receiving these drugs. Daily observations of temperature, skin, urine output and so forth, is desirable. White blood cell counts are especially valuable after the twelfth day of sulfa therapy.

Gradual sensitization seems to be produced by the sulfa drugs and particular care is required when the drugs must be administered a second or a third time if the patient has had a previous toxic reaction.

Evidence of toxicity calls for immediate discontinuance of the drug and the forcing of fluids. Of course fluids cannot be forced if there is evidence of renal or cardiac dysfunction. The purpose of forcing fluids is to hasten elimination of the sulfa drug, and this requires approximately four thousand cc. of fluids daily for at least five or six days.

If there is evidence of renal or cardiac failure attempt to produce a diuresis. The proctologist should always consult with the internist under such circumstances.

Anuria calls for consultation with the urologist. The hematoologist should always be made available if transfusion is required.

It should be remembered that most toxic sulfonamide reactions will clear spontaneously if the drug is stopped. Forcing fluids is the best therapeutic measure in most cases.

Toxic manifestations in antibiotic therapy include the drug fever of penicillin, headache, nausea and vomiting. However, the most common penicillin reactions are skin lesions. Such skin reactions appear in approximately five percent of all cases. These eruptions may be localized or generalized and exfoliating. They may occur within three hours of penicillin administration, or not until ten days after discontinuance of the drug. Skin reactions may occur alone or in conjunction with other evidences of general serum sickness such as nausea and vomiting and painful, swollen joints and glands. Myalgia may be excruciatingly severe.

Penicillin therapy must be discontinued unless the skin reactions are mild and localized. It will always be necessary to weigh the need for penicillin against the possible eventual toxic reactions. In most cases the proctologist will find it safest to discontinue the penicillin.

Benadryl or pyribenzamine may be employed in treatment of urticartial eruptions. If one hundred and fifty to two-hundred milligrams of these anti-histaminic drugs do not control urticaria it is best to discontinue penicillin therapy. These drugs should be continued for one week after antibiotic therapy has ceased.

The toxicity of streptomycin when employed locally in the dosage above indicated is limited. Certain patients do evidence a dermatitis, and in these cases the drug should be discontinued.

Streptomycin produces toxicity in about six per cent of all patients. Multiple courses of therapy (as with the sulfonamides and penicillin), are more apt to result in toxic reactions.

If streptomycin is continued for a prolonged period of time, as in tuberculous enteritis, deafness may be expected in about one percent of cases. This deafness may be permanent if the streptomycin is not stopped in time.

A very common reaction is vestibular dysfunction with vertigo. However, the dizziness may disappear as the therapy is continued.

Skin eruptions may appear during the second or third week of treatment, but treatment need not be discontinued unless they are generalized or exfoliating. Contact dermatitis may develop as a consequence of handling streptomycin just as it does in some cases after the handling of penicillin.

Streptomycin should be employed with care if there has been any evidence of impaired kidney function. This antibiotic commonly produces renal irritation.

Streptomycin may produce blood changes similar to those resulting from penicillin toxicity. Leukopenia and agranulocytosis have been reported. An eosinophilia as high as five percent frequently results from streptomycin therapy, but is of no consequence.

In general the proctologist must observe carefully for any evidence of toxicity when employing either a sulfonamide or an antibiotic. Pulse and temperature must be charted. Skin and mucus membranes of the mouth should be examined daily. A total white blood count is recommended, particularly after the twelfth day of sulfonamide therapy.

The hearing of patients receiving streptomycin should be observed daily by means of a simple watch test.

Urinary output should be charted, particularly if the patient is receiving sulfamerazine, sulfadiazine or sulfathiazole. If there is a definite decrease in urinary output it is best to consider immediate cessation of the sulfonamide.

Practical Clinical Applications

ULCERATIVE COLITIS: The specific etiology of ulcerative colitis is unknown. Specific therapy is therefore not possible. However, the poorly absorbed sulfa drugs, including sulfaguanidine, sulfasuxidine and sulfathaladine have been of apparent value. It may be that their major role lies in the control of secondary invaders. Until such time as a specific bacteria is demonstrated to be etiologic in any form of ulcerative colitis no function other than the above can be given to the sulfa drugs.

However, the control of secondary infection is important, and the decrease of colon bacterial flora probably assists in healing of ulcerations.

The dosage of sulfasuxidine is 0.25 gram per kilogram of body weight. This total dosage is given at once as the initial quantity, and is then divided in four daily doses given at four hour intervals. Sulfaguanidine is employed in a dosage of 4 grams every few hours day and night for approximately thirty days. The adult dosage of sulfathaladine is 1 gram every four hours day and night for thirty days.

It should be observed that the choice of the sulfonamide is not of particular importance in these patients. It would appear that any one of the poorly absorbed sulfonamides produces an equally favorable result. This would be expected if the drug action is merely one of reducing the activity of secondary invaders.

The same reduction of bacterial flora could be produced by the use of streptomycin orally. This, however, would be an expensive technique, and thus impractical.

BACILLARY DYSENTERY: Specific therapy in bacillary dysentery is possible with sulfadiazine or sulfamerazine. The initial dose of sulfadiazine is 0.1 gram per kilogram of body weight for patients weighing up to 50 kilograms. If the patient weighs more than 50 kilograms the initial dose of sulfadiazine should not be more than 5 grams. The maintenance dose for adults is 1 gram of sulfadiazine every four hours day and night. The maintenance dose for a child would be one sixth of the initial dose given at four hour intervals day and night.

The initial dose of sulfamerazine is 0.075 gram per kilogram of body weight up to a weight of 50 kilograms. The largest initial dose for patients over 50 kilograms in weight should be no more than 4 grams. The maintenance dose is one quarter of the initial dose at intervals of six to eight hours day and night.

Most cases will respond within four days, and dosage may be reduced by half after the first two days treatment. In very occasional severe cases sodium sulfadiazine may be employed parenterally as a five percent solution in sterile distilled water or in sterile isotonic sodium chloride solution. The initial intravenous dose of sodium sulfadiazine should be 0.1 gram per kilogram of body weight up to fifty kilograms of weight. The largest dose should not exceed 5 grams. The maintenance dose is 0.04 gram per kilogram of body weight given at intervals of six hours day and night.

Sodium sulfamerazine may be similarly prepared and given in an initial dose of 0.05 gram per kilogram of body weight for patients weighing under 50 kilograms. Above that weight the initial dose would be 2.5 grams. Maintenance dose calculation is based upon 0.025 gram per kilogram of body weight given at intervals of eight to twelve hours day and night.

General therapy in *diarrheal cases* has been outlined elsewhere.[2]

AMEBIASIS: The sulfa drugs and antibiotics are not effective against Endamoeba histolytica. However, evidence of amebiasis may be suppressed by adequate dosage with sulfaguanidine. Recurrence is prompt and amoebae reappear in the stool as soon as the drug is stopped.

Until further evidence is accumulated, therefore, to indicate especial value for sulfa or antibiotic therapy, it

It should always be recognized that the patient with gonorrheal proctitis may also have syphilis. The serology should be studied, and it must be remembered that the clinical history of the syphilis may be considerably altered by the penicillin treatment of the gonorrhea. Thus the serology for syphilis should be studied at monthly intervals for at least four months after the treament of gonorrhea.

SYPHILIS: The introduction of penicillin for the therapy of syphilis has resulted in a complete revision of our therapeutic concepts in this disease. However, the dosage recommendations are at such great variance that it is impossible eo establish specific schedules. Thus, the following recommendations are to be accepted only until adequate evidence has accumulated for a final evaluation.

The United States Public Health Service recommends the quick acting form of penicillin aqueous solution in total dosage of four million, eight hundred thousand units intramuscularly in individual injections of fifty thousand units every two hours day and night.

Another routine recommends forty thousand units of crystalline penicillin G intramuscularly every three hours day and night for a total of sixty injections.

Crystalline penicillin G in oil and beeswax takes second place in the treatment of early syphilis. Six hundred thousand units is the daily dosage and a total of six million units is recommended. There is no available information on the value of procaine penicillin G as a substitute for penicillin in oil and wax.

It is probably best for the proctologist to call for consultation in the therapy of syphilis. Expert assistance is required both for adequate diagnosis and for therapy, particularly when dealing wtih the early mucous lesion or chancre.

ABSCESS, FURUNCULOSIS AND CARBUNCLE: In all cases of localized infection adequate surgical drainage is the treatment of choice. Sulfa or antibiotic therapy may be employed only as adjuncts to proper surgical management.

The most frequent etiologic organisms in these conditions are the Staphylococcus aureus, the Streptococcus hemolyticus and the Escherichia coli. Crystalline penicillin G is of particular value if the abscess, carbuncle or furuncle is of staphylococcal origin. I prefer the aqueous procaine penicillin preparation in daily intramuscular dosage of three hundred thousand units. As indicated in the introductory discussion it is probably best to avoid topical application of either penicillin or the sulfa drugs. Hemolytic streptococcal infection requires either sulfadiazine or sulfamerazine in the dosage indicated in the introductory discussion. The same drugs are particularly effective in Escherichia coli infection.

The sulfa drugs will have served their objective within a few days after the institution of proper surgical drainage, and need not be continued beyond that time.

ERYSIPELAS: The Streptococcus hemolyticus responds promptly to sulfadiazine or sulfamerazine in the dosage indicated in the general discussion. The maintenance dose should be continued for several days after the infection has been brought under control. If the infection is so severe as to warrant supplementary penicillin therapy three hundred thousand units of aqueous procaine penicillin G may be given intramuscularly as daily dosage.

GAS GANGRENE: The surgical therapy of gas gangrene must be instituted at once. Treatment best combines sulfamerazine or sulfadiazine with penicillin. The sulfa dosage is as above described. The sulfa drugs are effective against the Clostridium welchii, the Clostridium septicum and the Clostridium sordelli but not against the Clostridium oedematiens.

It is best to employ crystalline penicillin G in five hundred thousand units dosage intravenously, followed by two hundred thousand units intramuscularly every two hours day and night.

Both penicillin and sulfa therapy should be continued at full dosage until the infection is well controlled. It is probably best to continue the sulfa therapy at half dosage for five to seven days after control of the infection. During this time single daily intramuscular aqueous procaine penicillin G injections of three hundred thousand units may be recommended.

DIVERTICULITIS: Sulfamerazine or sulfadiazine may be employed as supplementary therapy in acute diverticulitis. A blood concentration of six to eight milligrams per hundred cc. should be maintained. Penicillin is of no value in the therapy of diverticulitis peritonitis if the major offender is the Escherichia coli. This organism produces penicillinase which inactivates penicillin. In such cases streptomycin may be of value in a dosage of 0.3 gram at three hour intervals parenterally for approximately six days.

If colonic surgery is indicated the poorly absorbed sulfonamides may be employed both pre- and post-operatively. Sulfathaladine seems to be the drug of choice, and should be recommended in a dosage of 1 gram four times a day for five days pre-operatively. It should be continued for ten to fourteen days post-operatively. If the surgeon prefers sulfasuxadine or sulfaguanidine the dosage may be three grams at four hour intervals for the same period. The same principle of pre- and post-operative surgical preparation applies to all types of colonic surgery, and is not limited to the care of diverticulitis.

CONCLUSIONS: Sulfonamides and antibiotics are important additions to the therapeutic armamentarium of the proctologist. Dosage schedules, evidences of toxicity and their treatments, and specific applications in various forms of proctologic pathology have been detailed.

The limitations of sulfonamide and antibiotic therapy, as well as the applications have been discussed.

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Evaluation of Clinical Methods in Gastro-Intestinal Disease

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I. Role of Anamnesis, Age, Sex, Season and Gastric Acidity in Peptic Ulcer.

With the rapid progress made recently in the understanding of gastro-intestinal disease it appears worthwhile to pause a moment and consider how these newer concepts affect our routine study of G.I. patients. To pause that moment scientifically we studied gastric acidity, liver functions, cholesterol level and blood chemistry in G.I. Disease by review of private patients who had a very complete work-up, including these newer studies. Analysis of the results obtained permit us to express an opinion on what changes in our routine study of G.I. patients appear justified at present. This paper deals mainly with the question of the routine determination of gastric acidity. The other communications in this series are to be published in the future.

It has been our impression for many years that gastric analysis, either with the alcohol or Ewald test meal is not of great diagnostic significance in the routine study of gastro-intestinal disorders. Our experience in the recent war with army personnel strengthened this impression into a conviction that routine gastric analysis could be dispensed with, since only 53% of patients with positive evidence of ulcer demonstrated hyperacidity, the remainder showing hypoacidity or even achlorhydria.[1,2] Army experience thus showed that the most important use of gastric analysis,—the differential diagnosis of ulcer, was not based on fact. To see whether we could translate these findings to civilian practice we reviewed all the gastro-intestinal cases examined in 1945-1947 in the private practice of one of us (A.A.G.. and the late Dr. I. W. Held). This revealed interesting facts not only regarding the clinical value of routine gastric analysis but also the sex, age and seasonal incidence of the various gastro-intestinal diseases studied. Since the number of cases reviewed is large, it is considered worthwhile to report these incidental findings for comparison with the literature.

MATERIAL AND METHODS

While the predominant type of patient seen in our office and hospital practice falls into the two systems of gastro-intestinal and cardiovascular, other diseases in the field of internal medicine were also encountered. Of the 9,969 patients seen in the 3 year period (1945-1947), 3,330 (33%) could be classified as gastro-intestinal. 1,752 of these patients were diagnosed from history and physical examination alone as being functional in nature and not requiring the more detailed work-up (which will be described later). Of the 1,578 remaining cases that were worked up in detail, 441 were found suffering from a non-organic or functional condition, while 1,137 were placed in some organic gastro-intestional group. Table I shows the sub-division of these 1,137 cases under 15 clinical diagnosis, and a 16th group called "Miscellaneous."

All patients were interrogated with special elaboration of their gastro-intestinal complaints. The nervous history, particularly with respect to emotional disturbances and conflicts or economic uncertainties, was elicited. If the anamnesis and physical examination were of clinical significance, further examination was advised. This constituted gastro-intestinal fluoroscopy and X-rays, routine stool examination, complete blood count and gastric analysis (both fasting and 45 minutes after Ewald test meal). Achlorhydria was an indication for a repeat test meal after histamine injection. Proctoscopy and gastroscopy were performed when indicated. 24 hour fluoroscopy and X-rays, as well as barium enemas, were part of the roentgenological examination. The complete blood work-up included blood chemistry (especially total proteins, A-G ratio and cholesterol), serology, peripheral blood, and sed. rate.

RESULTS OF STUDY

The anamnesis is of importance generally to help one decide if the patient is suffering from a functional or organic condition. Of the total 9,969 patients examined, 3,330 presented gastrointestinal complaints. (33.4%) of the practice. It is interesting to note that practically 52.6% of the gastro-intestinal cases required no further examination to establish a clinical diagnosis. Of the remaining 1,578 patients who were examined by X-rays, etc., 441 or 27.9% proved to be functional, and 1,137 or 72.1% were of an organic nature. If one were to add these 441 cases proven to be functional after X-ray study to the 1,752 considered functional by history and physical examination alone, the total would

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DISEASE	10-19 yrs			20-29 yrs			30-39 yrs			40-49 yrs			50-59 yrs			60-69 yrs			70-79 yrs			TOTAL		
	M.	F.	C.	M.	F.	C.	M.	F.	C.	M.	F.	C.	M.	F.	C.	M.	F.	C.	M.	F.	C.	M.	F.	C.
1. Appendicular Disease	3	1	4	20	39	59	68	52	120	38	18	56	15	8	23	2	2	4	0	0	0	146	120	266
2. Duodenal Ulcer (Pos. Hist. & Pos. X-Ray)	2	1	3	24	7	31	58	12	70	51	7	58	4	1	5	2	0	2	0	0	0	141	28	169
3. Gall Bladder (Pos. Hist. & Post. X-Ray)	0	1	1	1	12	13	17	52	69	20	12	32	1	27	28	0	5	5	0	1	1	39	110	149
4. Duodenal Ulcer (Pos. Hist. & Neg. X-Ray)	3	0	3	9	9	18	27	7	34	20	3	23	6	3	9	2	1	3	0	0	0	67	23	90
5. Gall Bladder & Appendicular Disease	2	2	4	4	9	13	9	17	26	10	20	30	1	7	8	0	2	2	0	0	0	26	57	83
6. Adhesions	0	0	0	4	13	17	3	13	16	15	6	21	4	1	5	0	0	0	0	0	0	26	33	59
7. Gall Bladder (Neg. Hist. & Pos. X-Ray)	0	0	0	3	1	4	3	6	9	15	12	27	6	10	16	1	0	1	0	0	0	28	29	57
8. Duodenal Ulcer & Appendicular Disease	0	0	0	6	3	9	20	4	24	14	3	17	1	0	1	0	0	0	0	0	0	41	10	51
9. Stenosing Duodenal Ulcer	0	0	0	3	2	5	8	3	11	13	1	4	6	1	7	2	0	2	0	0	0	32	7	39
10. Gastric Ulcer	0	0	0	1	0	1	9	3	12	12	8	20	5	0	5	0	0	0	0	0	0	27	11	38
11. Ptosis	0	0	0	2	7	9	7	3	10	6	7	13	0	2	2	0	0	0	0	0	0	15	19	34
12. Duodenal Ulcer (Neg. Hist. & Pos. X-Ray)	0	0	0	1	0	1	8	1	9	6	2	8	3	3	6	4	1	5	2	0	2	24	7	31
13. Carcinoma	0	0	0	0	0	0	3	2	5	1	1	2	6	3	9	6	2	8	1	0	1	17	8	25
14. Diverticula	0	0	0	3	2	5	1	3	4	3	0	3	6	2	8	1	0	1	0	0	0	14	7	21
15. Ulcer & Gall Bladder	0	0	0	2	1	3	1	0	1	1	2	3	3	1	4	0	0	0	0	0	0	7	4	11
16. Miscellaneous, Jejunal ulcer, Gall Bladder, (Pos Hist. & Neg. X-Ray), Colitis	1	0	1	1	4	5	2	1	3	1	1	2	1	2	3	0	0	0	0	0	0	6	8	14
			16			193			423			329			139			33			4	656	481	1137

Table 1. Clinical Classification, Sex and Age Distribution of 1,137 Patients with Organic Gastro-Intestinal Disease Studied over a Three-Year Period (1945-1947).

be 2,193. Thus fully 65.9% of the gastro-intestinal cases were found suffering from a functional disorder and 34.1% (1,137 out of 3,330) from an organic condition.

Table I summarizes the important data,—classification, sex and age distribution of the 1,137 cases of an organic nature who were studied in detail: Of the total 1,137 cases 439 (38.6%) were peptic ulcer; 293 (25.9%) were gall bladder disease; 266 (23.4%) chronic appendix, the diagnosis in this group being based on criteria detailed in another communication[3]; while 25 (2.2%) were carcinoma. Almost 39% of the patients who had X ray studies proved to be suffering from peptic ulcer, as contrasted to the very low figure of malignancy (2%).

Table I shows further that of the 439 cases proven to be peptic ulcer 169 (40.3%) gave both a positive history and X-ray; 90 (21.4%) a positive history and negative X-ray; and 21 (5%) a negative history in the presence of a positive X-ray. 38 or 9% of the 439 cases of peptic ulcer were gastric. (27 males, 11 females).

SIGNIFICANCE OF ANAMNESIS

It is surprising how often one fails to encounter the typical anamnesis taught in medical schools and stated in text books. One must take cognizance of the fact that "atypical symptoms" may be obtained not at all suggestive of ulcer in the presence of positive roentgen findings. This was ascribed by the late Dr. I. W. Held and one of the authors (A. A. G.) to the peculiar constitution of the patient, which is atypical in its symptomatic response to local disease. [4,5]. If secretory disturbances predominate, excessive gastric secretion often causes persistent pyrosis and sour eructations. On the other hand, if sensory symptoms predominate, the characteristic radiation and duration may be lacking, still the pain may be so severe as to necessitate frequent administration of narcotics. In some cases symptoms of disturbed gastric motility are most troublesome with pronounced hyper-motility and gastrospasm. There is peristaltic unrest in the stomach, gnawing sensations of hunger, and a continuous desire to eat. There are cases where secretory,sensory and motor disturbances occur in the same patient varying in intensity at different times.

In general there are two types of atypical patients,—individuals of asthenic habitus, and of the hypersthenic.[5] The former is inclined to nervous symptoms and neurosis, while the latter is relatively indifferent to sensory disturbances and minimizes his complaints. In this era of psychosomatic medicine it is important for physicians to be ever alert to these varied manifestations of disease, relating the type of constitution to the patient's complaint. One must not forget, however, that just as there are ulcer patients with atypical symptoms or practically no symptoms at all, there are a greater number of psychoneurotic patients who present com-

plaints similar to the true ulcer patient, even though they are free of organic disease. This was particulary true in the armed forces, where anamnesis was often unreliable, while the X-rays were decisive in making the diagnosis. Two characteristics in the anamnesis of the psychoneurotic usually helped differentiate it from ulcer; namely, the lack of nocturnal pain, and the persistence of abdominal pain and discomfort even after ingestion of bland foods and alkalies. [2]

One notices on further study of Figure I that the male sex predominates in the chronic appendix series, while the female predominates in the realm of gall-bladder disease, especially in the 30-40 and 50-60 age group. Surprisingly enough, it is about equal in the 40-50 age group,—just the group of gall bladder cases we would expect to be predominantly female.

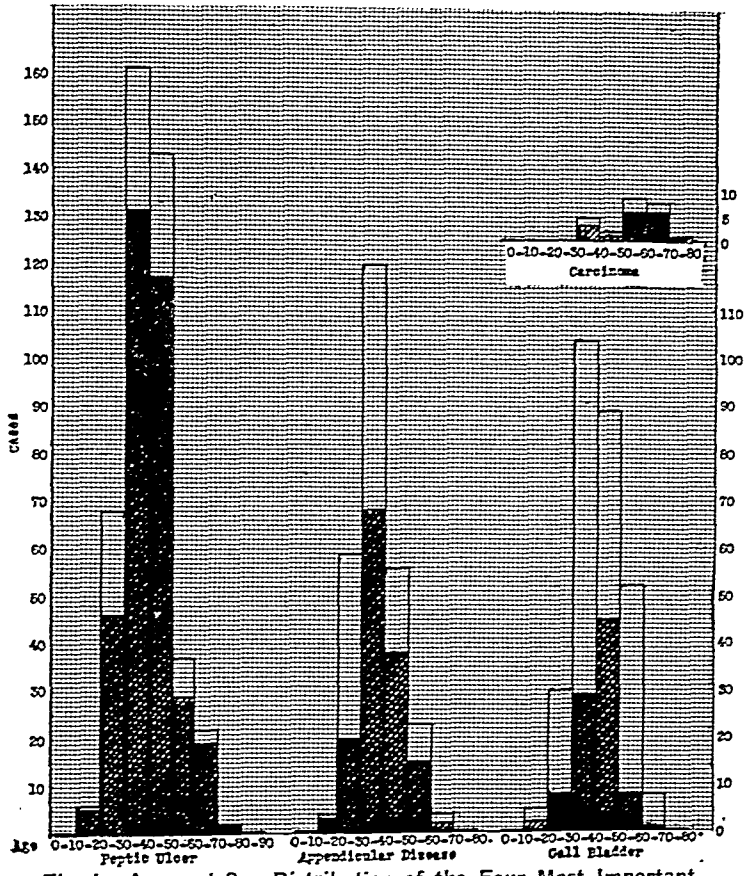


Fig. I. Age and Sex Distribution of the Four Most Important Organic Gastro-Intestinal Disease Groups. Males, shaded; females, clear.

SEX AND AGE INCIDENCE

There is a predominance of male (339 or 77.2%) over female (100 or 22.8%) in ulcer patients, as a study of Table I shows (demonstrated more strikingly in Figure I). This makes a ratio of approximately 3:4:1. The ratio is higher than that reported recently by Feldman [7] and similar to that obtained by Eusterman and Balfour in 1935. [8] Feldman believes that the war years have increased the frequency of peptic ulcer in women. This is doubtful, since the ratio of men to women seems to be about the same when the pre and post-war figures are compared. The war did not increase chronic peptic ulcer but made it appear more prevalent, because of the careful medical attention given to the armed forces. Whether the explanation for the predominance of male over female in peptic ulcer is neurogenic or endocrine is still a moot question.

SEASONAL INCIDENCE

An outstanding characteristic of the peptic ulcer anamnesis is the seasonal recurrence of the subjective complaints. We are accustomed to think of this as the spring and fall seasons. Figure II which shows the monthly incidence of the 4 most important groups of G.I. cases contradicts this dictum. The peak of peptic ulcer incidence is seen in June (summer) with a lesser rise in December-January (winter). The least number of peptic ulcer cases in our series is in March and November, contrary to Hutter [9] who found gastric ulcers more in cold seasons (December-February) and duodenal ulcers predominantly in May and late November.

We do believe there is a seasonal recurrence of the subjective complaints in the individual patient, yet we cannot be so dogmatic as to insist that it be at the same months of the year. One cannot deny the fact that neurogenic factors will precipitate a recurrence of com-

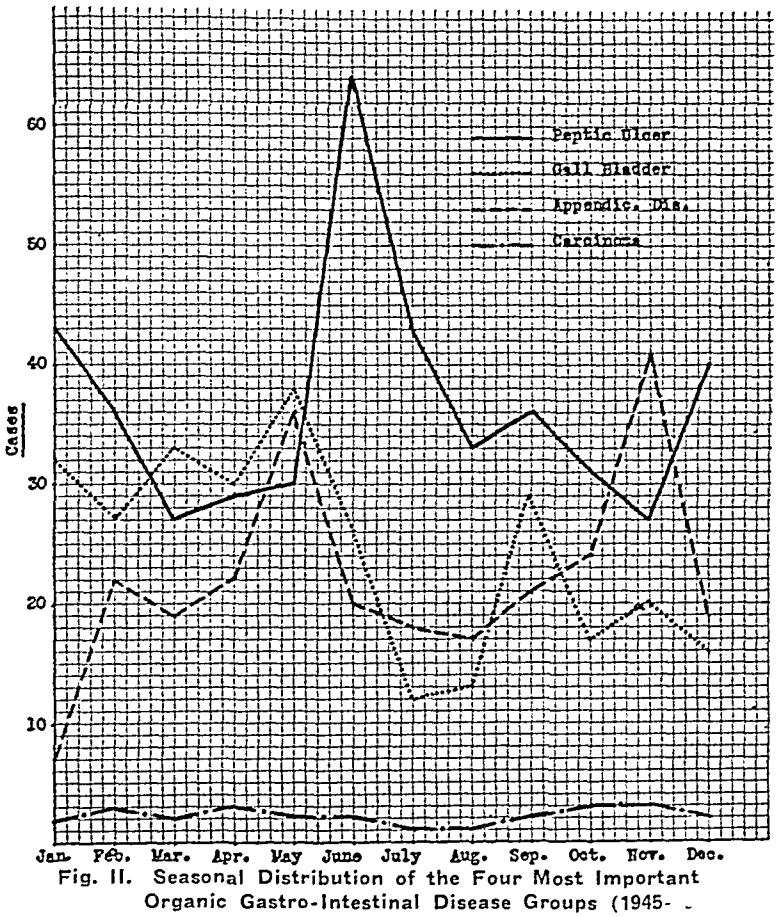


Fig. II. Seasonal Distribution of the Four Most Important Organic Gastro-Intestinal Disease Groups (1945-

plaints—whether it be emotional or economic, such as the uncertainty about the future. Such histories are common in our practice. An acute anxiety state may be the precipitating factor bringing the patient to the doctor. Wade Brown [10] showed organ-body relationships in ulcer, and stressed the fact that organ-balance

DISEASE	NUMBER			AGE			AVERAGE					
	M.	F.	C.	M.	F.	C.	M. Free Acid	F. Free Acid	C. Free Acid	M. Total Acid	F. Total Acid	C. Total Acid
1. Appendicular Disease	146	120	266	39.0	33.9	36.3	40.1	34.3	37.5	56.7	49.5	53.6
2. Duodenal Ulcer (Pos. Hist. & Pos. X-Ray)	141	28	169	38.0	34.0	37.4	46.0	45.6	46.1	62.4	58.9	61.9
3. Gall Bladder (Pos. Hist. & Pos. X-Ray)	39	110	149	40.0	40.9	40.6	33.0	32.0	32.3	50.2	49.5	49.6
4. Duodenal Ulcer (Pos. Hist. & Neg. X-Ray)	67	23	90	48.3	33.6	37.2	49.7	28.1	44.6	65.7	41.0	59.9
5. Gall Bladder & Appendicular Disease	26	57	83	37.0	41.1	39.9	38.0	31.5	33.4	55.1	48.4	50.3
6. Adhesions	26	33	59	38.6	31.5	34.5	38.5	34.2	36.0	53.5	52.6	53.0
7. Gall Bladder (Neg. Hist. & Pos. X-Ray)	28	29	57	42.0	45.8	44.0	38.2	43.1	40.7	51.0	62.9	57.3
8. Duodenal Ulcer & Appendicular Disease	41	10	51	36.6	34.0	36.1	41.4	48.3	42.6	55.7	68.7	58.0
9. Stenosing Duodenal Ulcer	32	7	39	43.5	32.0	41.9	52.5	27.5	48.9	67.8	44.0	64.4
10. Gastric Ulcer	27	11	38	44.3	41.8	43.5	41.0	44.2	42.0	59.0	64.5	60.0
11. Ptosis	15	19	34	42.2	36.7	38.7	44.0	36.4	39.2	59.5	50.9	54.0
12. Duodenal Ulcer (Neg. Hist. & Pos. X-Ray)	24	7	31	41.9	35.0	40.6	49.3	49.5	49.3	66.7	72.5	67.7
13. Carcinoma	17	8	25	53.6	46.7	51.1	28.0	16.0	23.5	44.6	29.7	39.6
14. Diverticula	14	7	21	44.0	38.0	41.4	42.5	18.3	32.1	60.7	31.0	49.4
15. Gall Bladder & Ulcer	7	4	11	42.5	43.0	42.7	39.0	51.0	43.0	54.0	84.0	64.0
16. Miscellaneous, Jejunal ulcer. Gall Badder (Pos. Hist. & Neg. X-Ray), Colitis	6	8	14	38.0	36.6	37.2	40.0	25.0	31.0	52.5	37.3	43.4
	656	481	1137	41.8	37.8	40.2	41.3	35.3	38.9	57.2	52.8	55.4

Table II. Average Free Acid and Total Acid Findings in 1,137 Cases of Organic G.I. Disease.

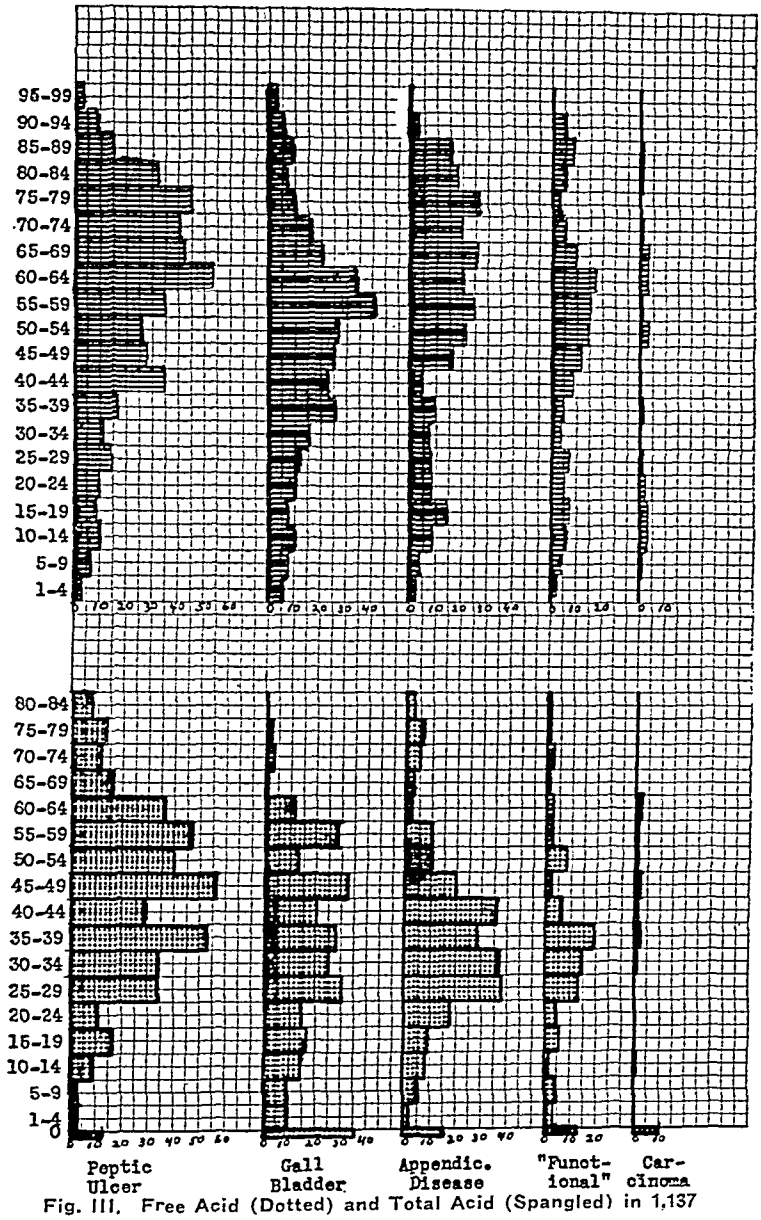


Fig. III. Free Acid (Dotted) and Total Acid (Spangled) in 1,137 Patients with Organic Gastro-Intestinal Disease.

	ULCER No. of Patients	GALL BLADDER No. of Patients	APPENDICULAR DISEASE No. of Patients	"FUNCTIONAL" (Adhesions, Ptosis, Diverticulae, Etc.) No. of Patients	CARCINOMA No. of Patients
Hyperacidity (above 40)	258 (58.8%)	113 (38.6%)	96 (36.1%)	30 (25.9%)	8 (32%)
Normal (15-40)	151 (34.4%)	113 (38.6%)	133 (50%)	61 (52.5%)	4 (16%)
Hypoacidity (below 15)	30 (6.8%)	67 (22.8%)	37 (13.9%)	25 (21.6%)	13 (52%)

Table III. Comparison of the Free Acid Findings in the Five Important Gastro-Intestional Disease Groups.

may differ in individuals by inheritance, or may vary from month to month and year to year. His observations furnish an explanation for the frequency of disease during certain seasons as well as the difference in reactions of individuals to various diseases in spring and fall.

With a final reference to Figure II, we note with interest how closely the incidence curves of peptic ulcer and gall bladder disease follow each other. Chronic appendicular disease shows a peak in May and November —carcinoma practically a straight line.

GASTRIC ACIDITY

A careful study of our results (Table II and Figure III) shows that the distribution of gastric acidity values is not characteristic enough for any of the diseases to be of important differential diagnostic value. Too many of the ulcer cases show hypoacidity, too many cancer cases show hyperacidity for us to consider these determinations helpful in differentiating these two conditions. Nor do we find any substantial differences in the acidity findings of the more serious organic disease groups (ulcer, appendix, gall bladder, cancer) as contrasted to the 116 cases of adhesions, ptosis, diverticuli and colitis which we grouped under "functional", since the disease processes are of a less serious and more functional nature. This fact is demonstrated more clearly in Table III which lists the free acidity findings in the 5 important G.I. disease groups under three divisions, normal (15-40), hypoacidity (below 15) and hyperacidity (above 40). 59% of the peptic ulcers show hyperacidity, 34% normal acidity and 7% hypoacidity. In the functional groups 26% showed hyperacidity, 52% normal acidity and 22% hypoacidity. It is of interest to note that only 23% of the gall bladder patients showed hypoacidity, 39% hyperacidity and 39% normal acidity, contrary to the general belief that hypoacidity is prevalent in gall bladder disease. Our figures fail to show then any characteristic gastric acidity findings that would indicate the usefulness of this determination in routine study of G.I. patients.

The results of the review of our civilian patients is thus similar to our findings in military personnel. In this connection it is worthwhile to quote typical figures of the results obtained in the study of dyspeptic soldiers in the last war (Table IV). It will be noted that a high percentage of hyperacidity was found in non-organic conditions, and was therefore not of much help differentiating ulcer from functional G.I disease. It is also important to note that psychoneurosis was of less frequency in the chronic peptic ulcer cases than in the functional. This is not in accord with other authors who claim that there is a high percentage of psychoneurosis in peptic ulcer patents. [11, 12, 13]

It may not be amiss to state at this point of the discussion that there is no uniformity of expert opinion on the role played by hyperacidity in producing and maintaining peptic ulcer. Although most investigators emphasize a tendency towards hyperacidity or hyperchlorhydria in peptic ulcer, [14] there are still two distinct and

Diagnosis	No. of Cases	Average Age, Yr.	Hyper-acidity, %	Average Length of Service, Mo.	Alcohol Habit* Degree	%	Average Duration of Symptoms Yr.	With Psycho-neurosis, %	Disposition Manner	% of Cases
Gastric ulcer	10	27.6	60	9	—	70	5.1	10	CDD	70
					+	30			D	10
					++	0			Tr	20
Duodenal ulcer	87	28.9		13	—	42	4.5	23	CDD	51
					+	41			D	13
					++	17			Tr	6
Gastroduodenitis	61	27.1	58	13	—	29	3.1	43	CDD	8
					+	40			D	80
					++	31			Tr	12
Functional dyspepsia	21	27.6	32	10	—	66	4.0	42	CDD	3
					+	30			D	94
					++	10			Tr	3
Psychoneurosis	18	27.5	44	8	—	82	5.5	100	CDD	25
					+	12			D	50
					++	6			Tr	25

*—, no history of alcoholism; +, moderate intake of alcohol; ++, excessive intake of alcohol.
CDD, certificate of disability for discharge; D, duty; Tr, transfer to a general hospital.

Table IV. Comparison of Pertinent Observations in 197 Dyspeptic Soldiers Studied in 1942-43. (From Held and Goldbloom's "Peptic Ulcer." P. 185. With Permission of the Publishers Charles C. Thomas, Springfield, Ill. 1946.

SUMMARY AND CONCLUSION

1. In this large series of gastro-intestinal patients seen in office and hospital practice (3,330 in a 3-year period) about 66% were of a functional character.
2. 39% of this series of 1,137 patients with organic gastro-intestinal disease revealed peptic ulcer. 26% gall bladder disease, 23% chronic appendix, 2% malignancy and 10% miscellaneous.
3. Of 439 cases proven to be peptic ulcer by full work-up (including X-rays), 40% gave a positive history with positive X-ray findings suggestive of peptic ulcer; 21% gave a positive history with negative X-rays while only 5% revealed positive X-ray evidence of ulcer in the presence of a non-suggestive history. This last group indicates that the history is not always pathognomonic of chronic peptic ulcer.
4. "Atypical symptoms" may be elicited from the patient's history, especially in certain constitutional types.
5. There is a 3.4:1 ratio of males to females in peptic ulcer. This was not increased by the war, since such ratios were also obtained in the pre-war era.
6. "Spring and fall" dictum of peptic ulcer recurrence was not found in our series of patients. Exacerbations of symptoms may depend upon a number of factors besides season, particularly neurogenic factors which produce emotional and mental conflicts.
7. Many factors of psychosomatic nature may be the 'trigger mechanism" in producing subjective symptoms simulating chronic peptic ulcer.
8. Gastric acidity values cannot be considered diagnostic of chronic peptic ulcer. Hyperacidity may frequently be found in functional conditions.
9. Routine gastric analysis should not be considered an indispensable laboratory test in the differential diagnosis of chronic peptic ulcer. It may be of value in certain cases, such as persistent achlorydria.

We are deeply indebted to the late Dr. I. W. Held for use of some of the data in this study and for his constant encouragement to put the newer concepts of clinical diagnosis to test on the best proving grounds available to us—our own private practices.

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Status of Health of the Natives of the Pribilof Islands As Determined by an Appointed Medical Commission

by

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and

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INTRODUCTION

The Office of the Secretary of the Interior requested that a medical commission be sent to the Pribilof Islands, Alaska, to investigate the cause or causes for the impairment of the health and dentition of the natives. The Pribilof group is made up mainly of two small islands, St. Paul and St. George, lying 240 miles north of Dutch Harbor in the Bering Sea. These islands are separated by 40 miles of water, and intercommunication is only by radio or boat.

The medical commissions* were organized, one in 1945 and one in 1946. These were comprised of both doctors and dentists. It was the aim of each commission to examine the nutrition, the physical condition, the dentition and the sanitation of the inhabitants of the Pribilofs. The Aleutian Islands were discovered by Bering in 1741. The Pribilof Islands were discovered in 1786 and were named for Pribilof, a Russian explorer, following his exploration in search of the great seal herd.[1] The natives of the Pribilofs are called Aleuts and are a branch of the Eskimo peoples. They are wards of the United Sates government and are under the direct supervision of the Department of Interior. The Department has been in control since 1911, following a treaty between Great Britain, Japan and the United States made for the purpose of controlling and propagating the great seal herd of the world. The duty of the Aleuts to the government, because of their particular ability, is to make proper selection of the seals for killing and to assist in shipping the valuable skins to the United States. The revenue derived annually from these furs greatly exceeds any necessary expenditures on the islands or the people thereof.

THE PLAN

One of the purposes of these commissions was to examine the eyes of the natives, and determine their need for glasses and the presence if any of communicable disease of the eyes. Secondly, a survey was to be made for the prevalence of tuberculosis, and the natives were scrutinized and screened for evidence of this disease. As will be pointed out, tuberculosis is a scourge on the Alaskan mainland. Diseases of the nose and throat were considered carefully, and tonsillectomies and adenoidectomies were performed when necessary, principally among the children.

The dentition of the Aleuts was examined, and an attempt was made to determine the cause for the early caries found in their teeth. Dentures were made for those persons requiring them. It was amazing to find that children in their early and middle teens needed full upper and lower dentures because of loss of their permanent teeth.

OPHTHALMOLOGY

The entire population of both St. Paul and St. George Islands was given thorough ophthalmological examinations, including refractions. Of the 356 natives examined, about 20% needed glasses for the correction of myopia. No communicable diseases of the eyes were found. Glaucoma was not present, and no operations were necessary.

TUBERCULOSIS SURVEY

It is a well-known fact that the rate for tuberculosis in Alaska is probably the highest in the world. The native population on the mainland is between 85,000 and 100,000 persons. The death rate from tuberculosis in Alaska was 359.1% per 100,000 for 1945-46. The rate for the United States during this period was 40.1%. These figures show the death rate from tuberculosis to be higher in Alaska than throughout the entire United States and territories, and to be nine times that of the forty-eight states. The high incidence of tuberculosis in Alaska may be due to many factors, among which can be cited poor housing facilities, crowded living conditions with lack of isolation, ignorance and lack of sanitary and hygienic education, undernourishment, and

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ing the foregoing three months. Their cooperation was excellent and the survey was made available for study.

It was readily seen that the diet of the Aleuts was made up chiefly of carbohydrates, particularly for the children, who buy candy and sweets from the stores rather than go home and eat normal well-balanced meals. From the list of foods submitted it was noted that the principal protein food available in the stores was bacon, which was purchased by only a dozen families out of three hundred. The second protein food, canned salmon, was purchased in moderate amounts by all families but when the number of cans of salmon used was compared with the number of persons in each family purchasing it, the amount of this protein food consumed was found to be less than that required for normal nutrition. Hunting was reported to be much better on St. Paul than on St. George, but, weather permitting, fishing is about equal on both islands. However, these sources of food are variable and unknown factors, and the meat and fish thus secured depend upon the energy and ambition of the individual as well as his skill and marksmanship when he goes out for game.

The literature today carries many reports as to the detrimental effects of large carbohydrate food intake on the dentition of our population. The effect may be more marked among the Aleuts when the fact is considered that they are primarily a meat eating people, and that in generations past they have followed a diet composed almost completely of seal, whale, walrus, meat, salmon, halibut and other fish available to them. Their physical make-up has been adapted to this type of protein intake for generations, but during the last half century the diet of these natives has become largely carbohydrate. The amount of seal meat they are permitted to preserve has even been restricted by the government.

By evolution the human body would certainly require more than one or two generations to alter itself so as to adapt to a carbohydrate diet rather than one composed largely of protein. It is believed therefore that this dietary change and the lack of necessary body adaptation are responsible for the condition of the teeth of the natives of the Pribilof Islands today. As has been pointed out, the older people have good teeth with little or no change in dentition. They were present before large carbohydrate stores were placed on the islands. Their dentition was formed and has been affected little by the alterations in diet. Science has proved that the teeth are affected by diet when they are laid down in utero. Hence the second generation shows much change in dentition as a result of the influence on these families of a carbohydrate diet, while the third generation shows an even greater change, with resulting caries and loss of teeth in the early teens.

The work of Belding[3] has pointed out that a diet largely carbohydrate in content may be instrumental in converting a harmless Streptococcus salivarius into a high acid producing mucoid phase. The shift from a protein to a carbohydrate diet may also alter the basal flora of the entire digestive tract. After this alteration has taken place, the caries producing factors become activated, and the growth of many acid producing oganisms, all of which contribute to the destruction of the teeth, is favored. Highly refined carbohydrate foods contribute further to the increase of caries. This fact has also been established by Belding. It is generally believed that the bacterial flora of primitive peoples differs from that of civilized adults. Basic requirements of food essentials may also differ in these two groups. It is therefore concluded that enforcement of a carbohydrate diet on the primitive Aleuts is responsible for the alterations in their dentition.

Ales Hrdlicka[4] of the United States National Museum, Washington, D. C., states: "Prolonged experience, ten seasons, with the people of Alaska and adjacent islands, supplemented by data from a truly great collection of well identified skeletal material of all times of the same region, shows that caries did not occur up to the time of the white man's mixing with the natives. In the Eskimo, caries gradually manifested itself during the last thirty years especially the last fifteen. Increase in caries among all present contingents of the native peoples in the far Northwest is due, in the author's opinion, to three causes which, in order of importance, are: (a) white man's food, especially cheap sweets, with half baked biscuits and bread; (b) constitutional and other debilitating diseases introduced by the white man; and (c) change in the habits and mode of living."

Price[5] in his conclusions states that: "Teeth respond earlier and with greater sensitivity to nutritional changes than other parts of the body, and at points of contact with modern civilization primitive man, discarding his own dietary habits and adopting the white man's forms of food having the least protective properties, loses immunity to caries."

One might go on further to quote Leigh[6], Levine[7], Rosebury[8], Siegel[9], and Waugh[10]. These workers have all indicated in their findings on the Eskimo and the Aleut that a change in diet has been largely responsible for the caries in the teeth of these people. Levine further points out that the Eskimo has not adopted the white man's food in toto, but only his poorest foods such as demineralized and devitaminized white flour, mineral free and vitamin free sugar, tea and coffee, which tend to reduce the Eskimo's intake of his own more protective foods.

Slow transportation and the absence of proper refrigeration are the two principle factors responsible for low standard of foods received on the Pribilof Islands. The distance is great, and travel from Seattle to the islands is difficult. Therefore the maintenance of a normal flow of food under adequate refrigeration to this point has met many obstacles. Until these shipping problems are solved, the foods shipped to these islands will continue to be of poor quality and principally carbohydrate in content. The commissions recommended that these factors be studied, and that transportation and refrigeration of foods be improved. It was further recommended that the protein content of the

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diet be increased to supplement the present carbohydrate diet.

The commissions discovered that the herd of cattle on St. Paul Island is grossly neglected, and that milk from these cattle is not utilized to its fullest capacity. As a result, this valuable ready-to-use food is simply wasted. It seems paradoxical that in this place, where animal conservation for human use is so magnificently practiced in the care of the great seal herd, proper care of the cattle, a ready source of protein food, is so glaringly neglected. It was therefore recommended by the commissions that this herd of cattle be utilized to its fullest extent, and that the natives be taught the use of milk in their diet.

SKIN TESTS

An experimental skin test was done on the Aleuts in an effort to determine the specificity of the two serums coccidioiden and histoplasmin. Both serums were provided through facilities of the National Institute of Health in Washington, D.C. At the time the natives were skin-tested with tuberculin, they were also given a 1/1000 dilution of histoplasmin and coccidioiden. A small group of the white population was used as attempted controls. The white persons had for the most part inhabited the southwestern or Pacific Coast states, or areas endemic to coccidioidosis. The natives had never been in the United States nor in areas endemic to either disease. All of the 356 natives skin-tested, except one, gave completely negative results for both serums. The one native whose test was positive, a female aged 31, showed a reaction of 3-plus to histoplasmin. She gave no history of contact with dogs or other animals. Incidentally no dogs are permitted on the islands, though there are several cats.

Of the 15 white persons tested, 3 gave positive reactions to coccidioiden. All 3 of these people had at some time been in the state of Kansas; 2 of them had lived in California, and the third was from Washington State. None of them gave history of having had the disease or of reactions indicative of having had the disease of sub-abute or sub-clinical type infection. From this work the conclusion is gained that natives living in an area not endemic to these infections showed no positive skin reactions (with one exception), while one-fifth of the white population, though small, showed positive reactions to coccidioiden. These tests may indicate the need for further study to determine the specificity of this type of skin tests.

SANITATION

The houses of the natives on both islands were visited and carefully inspected; and a great need was discovered for some kind of sewerage and indoor toilets. At present back houses are used, and the natives hang their seal meat on the sides of these houses to cure. Numerous flies, fur covered, are present in and about these back houses and feed on the seal meat as it hangs. This is an excellent method for transmission of disease, and the commissions could not comprehend the fact that these people had escaped severe epidemics thus far. It is indeed fortunate that no carriers of typhoid or paratyphoid have visited the islands. Outdoor steam baths are used for bathing. It is difficult to imagine even ourselves using such facilities in such cold weather. The suggestion was made that some type of indoor bath and toilet facilities be instituted, possibly using sea water, and that the natives be taught habits of cleanliness. The diseases of filth are in great evidence, but scabies, body lice, eczema and impetigo, which are the worst offenders, could be controlled with better habits and better laws of sanitation.

SUMMARY

A report has been submitted to the Department of Interior on the work of the commissions which were sent to the Pribilof Islands in 1945 and 1946. The recommendations of these commissions, as set forth in this article, are summarized here:

1. Adequate protection for the islands against tuberculosis, as outlined, has been set up.
2. The diet of the natives should be altered to contain a maximum of protein foods in order to prevent further destruction of their teeth. The high carbohydrate diet extensively used is believed to be the causative factor for caries in the teeth of the natives.
3. Adequate shipping and proper storage and refrigeration of foods must be provided so that meats and perishable foods may be made available.
4. The herd of cattle on the island should be given better care, and there should be an intelligent and adequate distribution of the available milk. Limited ranging is of course necessary to enforce normal sanitation.
5. Indoor bathing and toilet facilities should be installed in the houses, and a sanitary code should be established and supervised by the resident physician.
6. Further skin tests should be made with coccidioden and histoplasmin to determine the specificity of these serums.
7. The medical staff for the Pribilof Islands should be increased to include another physician, a nurse and a dentist. There is at present only one physician to provide medical care for the natives.

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NUTRITION

Relationship of Amino Acids To the Nutritive Value of Proteins

By

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INTRODUCTION: In 1816, Magendie published the results of his classical investigation dealing with the effects of nitrogen-free foods upon animals. He fed a 3-year old dog a nitrogen-free diet consisting of pure, white sugar and distilled water and observed that during the first week the animal maintained a cheerful disposition and apparently enjoyed his diet. During the second week, the dog lost weight, its appetite. and its gaiety. Its eyes became inflamed and ulcerated with concomitant heavy watery secretions. Emaciation and extreme weakness ensued despite a daily intake of three to four ounces of sugar. The animal died on the 32nd day and on autopsy, Magendie found that the carcass was devoid of fat, the skeletal muscles were reduced to almost one-sixth of their former weight. the stomach and viscera were also diminished in size and the urine was strongly alkaline. He appropriately concluded that there could be no animal life without nitrogenous food.

In 1839, when Mulder was expounding his theories on the nature of complex nitrogenous substances and coined the term "protein", Boussignault reported the results of the first experiment on record on nitrogen balance studies. Despite the tediousness of quantitative analytical procedure for nitrogen determination, he painstakingly worked out his experiment on a horse and a lactating cow and discovered that animals, unlike plants, cannot utilize atmospheric nitrogen (by nitrogen fixation) and that the nitrogen content of the excreta of animals does not exceed the nitrogen content of the food.

In 1852, Bidder and Schmidt repeated Boussignault's experiments and found that in the adult cat the nitrogen of the food could be precisely accounted for in the urine and feces. In 1866, Voit investigated the problem of nitrogen metabolism in the dog and revealed that, during starvation, if ample stores of fat existed in the body, there was relatively low nitrogen excretion; but immediately following the depletion of fat depots nitrogen excretion increased. He also investigated the effect of exercise on urea excretion and showed that fat dogs or animals receiving fat and carbohydrates did not have an augmented urea output during exercise but in the absence of these substances there was an increased urea output during inanition

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Voit's studies on the effects of high and low protein diets on nitrogen balance were also noteworthy. He demonstrated that dogs kept on low protein diets would invariably show positive nitrogen balance for the first few days when shifted to high protein diets, whereas dogs maintained on high protein diets would go into negative nitrogen balance for a like period when the regimen was altered to a lower protein intake.

The indispensability of protein in animal nutrition and its relation to nitrogen balance was universally acknowledged about the middle of the 19th century, despite the fact that there were sharp differences of opinion as to the exact functions and course of protein metabolism. Such men as Liebig and Pfluger and their students held on this subject certain dogmatic views that were irreconcilable with Voit's doctrine. Liebig considered protein as "plastic food" and fats and carbohydrates as "respiratory foods". His concept of nutrition was that nitrogenous foods were capable of being transmuted or converted into flesh and blood in the digestive tract and fats and carbohydrates supported the process of respiration. Liebig actually believed that the metabolism of protein formed the basis of muscular activity for he reasoned that since the main constituent of muscles was protein, the product metabolized during muscular contraction must be protein. Pfluger, who was constantly at odds with Voit, could not unshackle himself of Liebig's erroneous dogma. In 1891 he reluctantly admitted, that carbohydrate and fat might serve as the source of a part of muscle energy, but muscular contraction could not occur without some nitrogen loss.

The principle concerning the effects of nitrogenous food intake on nitrogen balance as conceived by Boussignault and elaborated by Voit and his school was soon enmeshed with intricate developments. In this connection we must bear in mind that the importance of amino acids in nutrition was in no way connected with protein metabolism and only a few amino acids had been known and their significance was obscure. The findings of investigators in this field noted that nitrogen equilibrium could be attained at various levels of protein and caloric intakes. These observations were most puzzling during that period. Voit conceived two types of proteins in the animal system. He regarded one type as "stable organ protein", to designate the constituent of the essential structures of the body that are not appreciably

TABLE I

Classification of the Amino Acids with Respect to their Growth Effects in the Rat.

INDISPENSABLE	DISPENSABLE	GROWTH ACCELERATOR
Histidine	Alanine	Arginine
Isoleucine	Aspartic Acid	Glutamic Acid
Leucine	Citrulline	Proline
Lysine	Glycine	Cystine
Methionine	Hydroxyproline	
Phenylalanine		
Threonine		Serine
Valine		Tyrosine

Rose's findings have been confirmed by others not only in the rat but in other species. Subsequently Rose (2) investigated man's amino acid requirements using highly purified diets in which he substituted pure amino acids for dietary nitrogen. He discovered that histidine is not essential to man. In order to determine just how much of each of the eight essentials is necessary to maintain nitrogen equilibrium. Rose investigated this problem and reported the upper limits of man's daily requirements. They are as follows:

TABLE II

Upper Limits of Man's Daily Requirements of Essential Amino Acids (2)

Amino Acid	Per Kg. Body Weight		For a 70 Kg-Man	
	A. A.	Nitrogen	A. A.	Nitrogen
	mg	mg	gm	gm
Isoleucine	42	4.50	2.94	0.315
Leucine	67	6.75	4.69	0.4725
Lysine	84	16.10	5.88	1.1127
Methionine	50	4.70	3.50	0.329
Phenylalanine	59	5.00	4.13	0.350
Threonine	42	4.95	2.94	0.3405
Tryptophane	26	3.57	1.82	0.250
Valine	59	7.05	4.13	0.4935
Total	429	52.62	30.03	3.6775

In his discussion of man's daily requirements of essential amino acids, Rose pointed out further that these estimates represent the highest possible values for a 70 kilogram man. The Committee on Food and Nutrition of the National Research Council recommended 70 gm of protein for a 70 kg. man, or one gram per kg of body weight. Assuming therefore that the protein intake of the diet is chiefly derived from casein, values are estimated by the author for each of the eight essential amino acids found in 70 gm and one gm of casein respectively. The figures are according to the best available data on the chemical composition of this protein (3). The calculated values and Rose's estimates are found in Table III.

On basis of nitrogen intake, a comparison is made between the nitrogen content of Rose's purified diet, that of Voit consisting of 118 gm of protein and that recommended by the Committee on Food and Nutrition of the National Research Council. The data are found in Table IV.

TABLE III

Comparison Between the Upper Limits of the Eight Essential Amino Acids As Recommended by Rose and as Found in One Gram and in 70 Gram of Casein.

Amino Acids	Per Kg Body Weight		For a 70 Kg Man	
	Rose	1 gm Casein	Rose	70 gm Casein
	Mg	Mg	Gm	Gm
Isoleucine	42	59	2.94	4.13
Leucine	67	95	4.69	6.65
Lysine	84	78	5.88	5.46
Methionine	50	30	3.50	2.10
Phenylalanine	59	51	4.13	3.57
Threonine	42	40	2.94	2.80
Tryptophane	26	12	1.82	0.84
Valine	59	65	4.13	4.55
Total	429	430	30.03	30.10

TABLE IV

Protein or Amino Acids Intake and Dietary Nitrogen per Kg of Body Weight and for a 70 Kg man.

According to	Protein or Amino Acids Intake		Nitrogen Intake	
	Total	Per Kg	Total	Per Kg
	Gm	Gm	Gm	Gm
Rose	30.03	0.429	3.675	0.052
Voit	118.00	1.69	18.90	0.270
Committee on Food and Nutrition—N.R.C.	70.00	1.00	11.20	0.160

In the light of our present knowledge of protein nutrition, Voit's standard of 118 gm of protein intake for a 70 kg man is indeed too high and there can be no further justification for this allowance to the healthy normal human being.

By deleting the non-essential amino acids from the diet recommended by the Committee on Food and Nutrition of the National Research Council, values for the indispensable amino acids content of casein seem to be in harmony with those of Rose. Rose's recommendation of a high estimate for methionine is justifiable since his purified diet does not contain any cystine and in the absence of the latter, methionine assumes all the prerogatives of cystine in the body.

Further studies on man's daily requirement of tryptophane (2) indicate that the minimum level compatible with consistent nitrogen balance is about 0.15 gm. with a recommendation to permit an allowance of 0.30 gm. Rose states: "Obviously, it would not be a safe procedure, under ordinary dietary conditions, to administer the minimum amount of any essential, since some variation in the requirement may occur under special circumstances or in different individuals. Reason dictates that in so important a matter as the formulation of an adequate diet provision be made for an appropriate excess of each indispensable constituent. In all probability we shall recommend eventually that the daily intakes of the essential amino acids exceed the minima by 100 per cent. This would appear to provide a sufficient 'factor of safety' for all contingencies, at least in normal individuals. That this applies to tryptophane is indicated by the fact that eighteen different individuals have been kept in nitrogen balance upon daily intakes of 0.3 gm or less."

On careful examination of these purified diets in which nitrogen balance is obtained by substituting the essential amino acids for dietary protein, one wonders as to whether or not the non-essential amino acids which comprise more than 50 per cent of the remainder of the constituents of protein have any significance at all. It is indeed hazardous to state categorically that the animal system can entirely dispense with them. There is every reason to believe that some of them do play some important functions in metabolism and their continued absence from the diet may lead to some deleterious effects of which we have not as yet been able to secure tangible evidence. The omission of tyrosine for example would necessitate increasing the minimum requirement of phenylalanine and the absence of cystine must be compensated for by additional amounts of methionine. It is also possible that the liver, if it should be proven to be the only site of synthesis of amino acids, would have to work much harder and a slowing down of anabolism might ensue. In effect there is still much discrepancy between the rate of growth observed in rats kept on protein diets and those kept on purified diets. The rate of growth observed is less in the latter group than in the former. (See Figure 1).

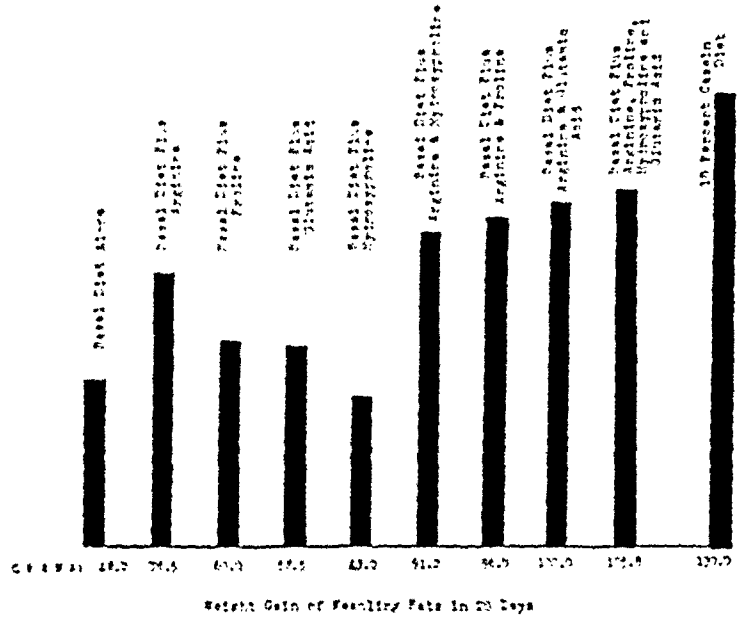


FIGURE 1

GROWTH ACCELERATOR — AMINO ACIDS:

Weil-Malherbe and Krebs (4) succeeded in demonstrating that alpha-ketoglutaric acid is formed by the action of kidney slices on proline. Neber (5) employing a similar technique involving the use of liver slices, isolated glutamic acid. Krebs (6) next showed that mammalian kidney extract transforms both D-proline and D-orinithine into alpha-keto-delta-aminovaleric acid. Subsequent to these investigations, Schoenheimer and his associates (7,8) using the mouse, brilliantly demonstrated in a series of experiments involving the use of isotopic amino acids that deuteroornithine is converted into deuteroarginine, deuteroproline and deuteroglutamic acid. In another investigation, it was shown (9) that proline containing both deuterium and N^{15} is transformed by the rat into isotopic hydroxyproline, arginine and glutamic acid.

In view of the above intimate interconversion-relationship of these amino acids, Womack and Rose (10) studied the nutritional significance of arginine, proline, glutamic acid and hydroxyproline in the growing rat. They used, for control, a complete basal diet in which a mixture of the 9 amino acids essential to the rat served as the chief source of dietary nitrogen. Male weanling rats were selected as the experimental subjects and these were divided into several groups. One group received the basal diet alone while others were given in addition either arginine or proline or glutamic acid or hydroxyproline alone. Then in another similar study they investigated the effects of different combination of these four amino acids. Their results are graphically represented in Figure I.

One can clearly see from the preceding data that on a basal diet comprising only a mixture of 9 essential amino acids as the sole source of dietary nitrogen, there was only a fair promotion of growth, but not as one would expect from a diet containing a protein such as casein or lactalbumin. Obviously these investigators were not interested in making this comparison as this discrepancy is well known. However, when the basal diet was supplemented with each of arginine, proline or glutamic acid alone, there was a decided increment in growth above that of the basal diet. This increment became indeed more vivid when the supplement contained a mixture of the four amino acids involved. Such a growth-stimulating effect cannot be disregarded. Furthermore, it might indeed have been difficult to detect

if adult, instead of weanling rats, had been used, or nitrogen balance studies were the only criteria. Of these four amino acids, hydroxyproline appears to promote no growth-stimulating effect, in fact when incorporated alone in the basal diet (in fairly large amounts) it seems to exert some inhibitory effect.

It is too early to conclude from the above and other experiments on record as to whether or not there would be any deleterious effect or some significant histopathologic changes in certain organs of the animal system as the liver, kidneys, heart, etc., as a consequence of the constant omission from the daily diet of the amino acids in the "growth-accelerator" group or even in the dispensable class.

SUPPLEMENTATION: Man's daily diet is not limited to one type of protein. Even an infant's diet which consists mainly of human's or cow's milk contains at least two types, viz.: casein and lactalbumin, and these two proteins differ markedly from one another in their respective biologic values, hence in their amino-acid composition. The estimation of the essential amino acids of man's diets that vary not only from day to day but several times daily, is impracticable and a very difficult task. However, on the basis of our present knowledge of nutritive aspects of proteins in foodstuffs we have amassed a fair amount of information on their respective biologic values and we have recognized not only marked deficiencies in many of them but learned how to circumvent such deficiencies.

For the correction of deficient foodstuffs, it is important to know their composition with respect to their essential amino-acid content. Improvement in nutritive value of such substances can then be accomplished either by combining the deficient protein with another protein that contains the missing amino acid or by supplementing the amino acid it lacks. Supplementation of proteins with essential amino acids is simple and economical and is in no way hazardous to human life. In this connection, it must be clearly pointed out that these components of proteins *are not stored in the body*. The intake of any short of a complete mixture results in nutritive failure.

The synthesis of cellular protein in the animal system requires therefore the availability at one time of all components in suitable proportions. In other words all-or-non principle seems to prevail. Those components that are not utilized for the synthesis of tissue proteins are deaminized and the carbon chains of their molecules are used as a source of energy or converted into carbohydrate or fat.

Berg and Rose (11) fed a tryptophane-deficient diet to young rats and showed better growth when the tryptophane supplement was given in divided doses than all at one time. One may conclude from these findings that (1) the administration of a single dose of tryptophane supplement along with the deficient diet resulted in having a portion of this amino acid more rapidly absorbed prior to the liberation of other amino acids from dietary protein that is undergoing digestion; hence an uneven distribution of amino acids in circulaton. (2) The portion of tryptophane which was more rapidly absorbed must have undergone metabolism thus leaving inadequate amounts to supply the deficiency and satisfy growth requirement. Elman (12) intravenously administered tryptophane-free acid digest of casein into humans and six hours later the tryptophane supplement. He reported poor utilization as compared with the intravenous administration of acid hydrolysate of casein fortified with tryptophane. Geiger (13) fed young rats rations deficient in tryptophane, methionine or lysine and also observed poor growth when the deficient amino acid was fed six and 12 hours later. Cannon and co-workers (14) made a careful study of the effect of feeding protein-depleted rats complete mixture of amino acids as protein substitute in the diet. They reported: "If the basal ration was divided into two portions, to one of which was added an amino acid mixture composed of arginine, histidine, leucine, lysine and threonine, and to the other a mixture composed of isoleucine, methionine, phenylalanine, tryptophane and valine and these two rations were fed alternately at hourly periods with an hourly fasting period between each feeding, the animals continued to lose weight. When however, the two incomplete rations were combined and fed under similar conditions, weight recovery was immediate. These experiments suggest, therefore, that for effective tissue synthesis all essential amino acids must be available in the tissues practically simultaneously; otherwise the first group absorbed is not stored long enough to enable its essential amino acids to combine with those of the second group for the synthesis of complete tissue proteins."

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Nutrition Notes

Vitamin Requirements of Human Adults

The Report of the Vitamin A Sub-Committee of the Accessory Food Factors Committee of the National Research Council in Britain, was released March 11, 1949, and may be obtained from the British Library of Information, 50 Rockefeller Plaza, New York, N.Y., for approximately 75 cents plus mailing costs. The Sub-Committee on Vitamin A was headed by Sir Edward Mellanby, G.B.E., K.C.B., M.D., SC.D., F.R.C.S., F.R.S. This is a highly instructive report, one of the surprising features of which is the extreme difficulty of producing symptoms of Vitamin A deprivation in human beings, within a two year period of dieting. The investigation was made on volunteer conscientious objectors at the Sorby Research Institute, 23 men and 3 women, mostly between the ages of 20 and 30 years cooperating in it.

The plan adopted was to give 16 of them a diet virtually devoid of vitamin A and carotene until unmistakable signs of deficiency appeared and then to determine what dose of vitamin A or carotene was needed to insure recovery to normal. The remaining 7 volunteers served as positive controls, receiving the same diet as the main group, but with a prophylactic supplement of either vitamin A or carotene from various sources. The experiment began in 1942 and lasted two years, and even at the end of this time not all the original expectations had been realized. At the end of eight months of deprivation there was still no discernible change in the volunteers beyond a lowering of the blood carotenoids; this, though useless as a criterion of depletion, was at least evidence that the diet was not being evaded.

Gradually there began to appear a drop in the vitamin A level of the plasma and a deterioration in the capacity for dark adaptation, the two changes that proved to be the *only reliable criterion of depletion.* By these criteria, no more than 3 men could be judged unmistakably deficient and hence suitable for therapeutic tests, although several of the volunteers persisted with the diet for more than 18 months and one for over two years. No other unequivocal signs of deficiency were found in any of the 16 deprived subjects at any time during the whole course of the experiment. Such abnormalities as follicular hyperkeratosis, conjunctival degenerations or undue fatigue—all commonly thought to be associated with vitamin A deficiency — were either absent or equally present in the deprived and the non-deprived, or present in the same subjects both before and after depletion. It is clear that vitamin A deficiency is much less easily or rapidly induced in hitherto well-fed adults than has been previously supposed. This conclusion is of practical importance, but it must not be overlooked that the scope of this experiment was restricted, and its results are not applicable to the needs of children, pregnant or nursing mothers, or the chronically undernourished. It is the negative conclusions of the experiment and a sense of the complexity inseparable from all such studies on human beings that are the dominant impressions left by a study of this report. The positive findings were too scanty to justify a precise estimate of the requirement of vitamin A or carotene, and the tentative recommendations subsequently made by the Sub-Committee allow a generous margin of safety and do not conflict with previous authoritative opinion. Emphasis is laid upon the wide differences in the availability of carotene from various sources and the consequent undesirability of fixing any single figure for the carotene requirement. Much of the interest of this elaborate report is to be found in the detailed descriptions of experimental technique and apparatus. Among the new developments may be mentioned Livingstone's method of rod scotometry, which promises to provide a sensitive gauge of impaired night vision.

The first result of the deficient diet was a marked drop in the carotenoid content of the blood. Within three months, the initial average value of about 150 I.U. fell to about 40 I.U. per 100 ml. Most, if not all of this residual carotenoid content was made up of substances other than alpha- and beta-carotene. The normal level of vitamin A in blood appears to be about 120 I.U. per ml. In 4 subjects the fall became very pronounced and levels below 50 I.U. vitamin A per 100 ml. were reached. One man, however, showed no appreciable drop even after 22 months of deprivation. In 3 subjects whose dark adaptation deteriorated significantly there were low average plasma vitamin A values at the critical time. A fall of the average value to below 50 I.U. per 100 ml. occurred a few weeks earlier. The conclusion was reached, as a result of treating depleted cases, that the minimum protective dose of carotene is about 1500 I.U. daily and the figure of 3000 I.U. daily is put forward as the value for the requirement to cover individual variations and to leave a margin of safety, on the supposition that 100 per cent of the carotene is available.

If a single value is put forward for the daily requirement for carotene, it is suggested by the Sub-Committee that this should be 7500 I.U., as being three times the daily requirement of vitamin A, and as being a figure roughly representative for the different sources of carotene in the diet. In the case of vitamin A concentrate, a daily requirement of 2500 I.U. seems to have been established.

It was found that the plasma level of vitamin A was not affected by the consumption of alcohol. The capacity for dark adapation was not improved and in some cases reduced by alcohol intake. In vitamin A deficient subjects the time required for the maximum dark adaptation was found to be much longer than the 30 minutes usually sufficient for reaching the true final rod threshold of normal subjects, and might improve continually for many hours. The final rod threshold of the deprived subjects as measured by the adaptometer of Wald, showed a slight but definite "seasonal" deterioration during the winter seasons of 1942-43 and 1943-44, and it appears that the deterioration par-

alleled the atmospheric temperature. The possibility of the synthesis of carotene in the human intestine was considered. It was confirmed that the pigments of *Staphylococcus aureus* include alpha- and beta-carotene but the available evidence is against a synthesis of carotene by the micro-organisms of the intestine in the subjects of the experiment.

How to Feed the People in War Time

Although America, because of her bountiful agricultural resources, was able to maintain reasonable standards of nutrition during World War II, it does not necessarily follow that we would be capable of similar success in a future war, because it is always possible that such a war might last too long and throw too great a strain upon our resources, as well as our ingenuity. Previous wars have, fortunately, always had a point of termination, caused essentially by the economic and man-power exhaustion of one of the belligerents. Much was learned in World War II respecting this aspect of national fatigue, and it is likely, in case of a future international conflict, that all belligerents would at once place their respective economies on a total war basis, with *all* energies focused on the military objective, and all men, women and children converted to virtual soldier status. No other solution is available. One of the most important elements in such a war would be the preservation of nutrition at a level sufficiently high as to maintain efficiency and morale, but this is a very special problem.

The problem of maintaining a satisfactory nutritional level both for the armed services and the civilian population involves many thousands of considerations, among which the chief are agricultural production, fertilizer supply, stock-piling of foods, transportation, rationing, price controls, and special group requirements. There is also the important problem of rendering each local geographic area semi-independent in case of isolation by an invading force. Finally there is the likelihood that America would be required to feed one or more of her allies during the period of protracted hostilities. Communal feeding would unquestionably be adopted in urban areas, because of its economic possibilities and the direct control of food hygiene in cooking. All waste of food would be prohibited by law. A careful physical check-up on the civilian population would be necessary and the simple operation of *weighing* the individual on a pair of scales is, as Leone* points out, the chief and most significant operation involved. He also states that while a minimum of 1500 calories per day, per individual is necessary, this may be augmented by bread and potatoes which ought not to be rationed. The vitamin and mineral content of the diet must also be kept in mind and the recommendations of the daily allowances by the National Research Council form the basis of this aspect of the problem. Fish is another item which ought not be rationed, and provides a fair source of protein under emergency conditions. All black markets and all adulterations of foods would require complete control by the extension of present laws. The accumulation of vast quantities of powdered milk should be undertaken as rapidly as possible, inasmuch as it is the best source of biologically valuable protein. Special allocation of food to hospitals and orphanages is important, and children must be given first call upon food supplies to ensure the vitality of the rising generation who must take over the responsibilities of a later resumption of significant civil aims, once the conflict is terminated. Osborn, in his book *"Our Plundered Planet"* has indicated that the cultivable areas of the earth in relation to population are now so limited that there are less than two acres available per person, and this is not sufficient to meet the demands of a growing world population, whose living standards are becoming increasingly high. Thus, the eventual nutritional problems of *homo sapiens* promise to be nearly as acute as those which would be presented to us by any new international war that should last longer than three or four years.

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Abstracts on Nutrition

PATEL, J. C.: *Crystalline anti-pernicious anemia factor in treatment of two cases of tropical macrocytic anemia.* (Brit. Med. J., Nov. 27, 1948, 934--935).

Lester Smith and Parker in 1948 isolated a red crystalline substance from liver which produced similar good results on the hematologic and neurologic phases of pernicious anemia as were obtained by the use of vitamin B_{12} isolated in America by Rickes, Brink, Koniuszy, Wood and Folkers. Vitamin B_{12} was found effective by Spies et al in pernicious anemia, nutritional macrocytic anemia and non-tropical sprue, as well as in tropical sprue. Lester Smith's red crystalline material produced satisfactory hematological and neurological responses in pernicious anemia, although a case of megaloblastic anemia of pregnancy which failed to respond to Smith's material did later respond to folic acid. The present paper records 2 cases of tropical macrocytic anemia, which is thought to be due to the lack of extrinsic factor, which both responded promptly to Smith's material, in the amount of 80 micrograms each.

CHAUDHURT, R. N.: *Diet in typhoid fever.* (Journal Indian Med. Assoc., Nov., 1948, Vol. 18, No. 2, 43-47).

This is a plea for feeding typhoid patients as nearly a normal diet as possible and the author believes that the extreme emaciation commonly accompanying the disease is due chiefly to starvation. He finds that a positive nitrogen balance may be obtained if sufficient food is fed. Where anorexia is extreme, the intravenous route may be used. Proper feeding may be accomplish-

ed in 90 percent of cases and the patients tolerate it well. Adjustments must be made in the presence of distressing gastrointestinal symptoms such as tympanites or diarrhea. Dehydration may be overcome by intravenous 5 percent glucose. Plasma transfusions are required to meet the metabolic requirements of the patients in acute stages and produce strikingly *good* results by combatting the effects of medical shock. In case of hemorrhage food is withheld for 24 hours, and during this time blood or plasma transfusions are used, as well as vitamin K. Such treatment transforms the general aspects of the disease.

HALL, B. E., MORGAN, E. H.: *Oral administration of vitamin B_{12} in pernicious anemia. I. Presence of intrinsic factor in Berkefeld-filtered pooled human gastric juice; preliminary report.* (Proc. Staff Meet. Mayo Clin., Vol. 24 No. 4, Feb. 16, 1949, 99-107).

It was found that the weekly oral administration of 25 to 35 micrograms of vitamin B_{12} alone to patients having pernicious anemia in relapse, fails to induce an hematopoietic response. Similarly, the daily oral administration of 150 c.c. Berkefeld-filtered pooled human gastric juice is devoid of hematopoietic activity on the patient who has pernicious anemia. When gastric juice obtained from patients having uncomplicated duodenal ulcer or functional complaints referable to the gastrointestinal tract is administered simultaneously with or within two hours of the oral administration of vitamin B_{12} an hematopoietic response occurs. Gastric juice obtained from these sources and passed through a Berkefeld filter, therefore, must contain the intrinsic factor. The minimal daily quantity of gastric juice required to potentiate an optimal hematopoietic response from 5 micrograms of vitamin B_{12} administered orally to patients with pernicious anemia in relapse lies somewhere between 25 and 150 c.c. This work makes it appear that vitamin B_{12} is the actual extrinsic factor. Castle confirmed, in a personal communication to the authors, that the intrinsic factor is not removed by Berkefeld-filtration. Heinle and Miller in 1939 reported that the intravenous administration of Berkefeld-filtered neutralized gastric juice to 2 patients with pernicious anemia in relapse did not evoke an hematopoietic response in either case presumably because no extrinsic factor as such was present in the blood stream or other parenteral sites to enable a reaction to take place, or that insufficient of the intrinsic factor was introduced. Whether intrinsic factor is necessary in the upper intestine to permit *absorption* of orally administered vitamin B_{12} or whether it is needed to *react* with the vitamin B_{12} to form an altered product is uncertain. The reviewer's reaction would favor the former hypothesis since we know that the parenteral administration of vitamin B_{12} invariably produces a good blood response, and there is no reason to think that the intrinsic factor is represented in any parenteral site, although it *could possibly* be represented in the liver or elsewhere for all we know. It is too soon, as the authors state, to conclude that vitamin B_{12} is ineffective when orally administered, until much larger oral doses have been employed.

MADDEN, S. C.: *Amino-acids in the production of plasma protein and nitrogen balance.* (Rev. Gastroent., March, 1949, Vol. 16, No. 3, 218-219).

All amino-acid constituents of the human body can be formed by the body except the following:—threonine, valine, leucine, isoleucine, tryptophane, lysin, phenylalanine and methionine. If these latter are absent in the diet, nitrogen imbalance occurs. It is important to feed sick persons for this reason, and also because, otherwise, the body's ability to form some of the other amino-acids may be strained. A nitrogen imbalance may be overcome by the injection of human plasma, and by feeding or injection of purified serum albumin, or by the intake of essential aminoacids, and such procedures will produce plasma protein. Infants need at least 15 times as much tryptophane as adults. While intravenous injection of aminoacid solutions often are needed in emergencies, yet nitrogen balance is greater in humans with oral than with intravenous feeding of the same amino-acid mixtures.

WALDENSTROM, J. AND ANDER, L.: *Folic acid treatment.* (Nordisk Med., Nov. 19, 1948, Vol. 40, No. 47, 2134-2137).

The use of folic acid in pernicious anemia patients, in the hands of the author, proved somewhat more satisfactory than it has generally been regarded. In 25 patients he observed only one definite neurological relapse while taking folic acid and, in this case, liver extract had to be resorted to. He feels that these results may be due to the fact that in Uppsala, Sweden, neurological complications are somewhat rare. He is not in favor of folic acid treatment of P.A. unless the patient is under the closest neurological observation. A small number of patients with liver-refractory anemia of megaloblastic type reacted well to folic acid and in one case the effect was definitely life-saving. Patients with hemolytic or aplastic anemia did not react to treatment with folic acid.

TAYLOR, G. F., CHHUTTANI, P. N. AND KUMAR, S.: *The meat ration and blood levels: investigation of Indian soldiers in Persia and Iraq, 1944.* (Brit. Med. J., Feb. 5, 1949).

Hematological investigation of a group of vegetarian and a group of meat-eating Indian soldiers doing full duty in a desert garrison of about 17,000 meat eaters and 1,188 vegetarians, the latter of whom showed a high hospital admission rate due to nutritional macrocytic anemia, revealed that the vegetarians showed, on the average, a statistically significant lower blood level, with macrocytosis. A number were suffering from frank nutritional macrocytic anemia. The vegetarians' sternal-marrow nucleated red-cell percentages were also significantly different from those of the meat-eaters and had a high megaloblast-erythroblast level. In the absence of any constant etiological factor other than the diet, the hematological differences were concluded to be due to the lack of the weekly ration of 20 ounces of fresh mutton in the vegetarians' diet and the consequent insufficiency of hematopoietic requirements. The daily rations contained over 3,000 calories and over 80 grams

of vegetable protein. This indicates that under conditions of hard physical work, diet alone, unassisted by precipitating coincidental diseases, could bring about a frank nutritional macrocytic anemia. There was suggestive evidence of widespread iron deficiency in both groups.

Editorial

THE HISTORY OF GASTROENTEROLOGY

Cicero said, "Not to know what has transpired in former times is to continue always a child." History, itself a great stimulant and staff of courage, strengthens and visualizes the future by virtue of its eternity. Medical history differs from all others in that it rarely repeats itself. The history of the development of medicine in all branches has shown that it is a series of detached, basic facts, eventually assimilated into a routine of practice. Gastroenterology is a definite field of medical work, investigation and research based upon a multiplication of these facts.

It would be worthwhile, however, to review briefly at the outset the significant accomplishments of the pioneers in this field. We do this not so much in the role of historian looking backward, but as prophet casting luminous rays ahead.

The origin of Gastroenterology may be said to have occurred in Italy, Germany and the United States. In 1780, Spallanzani proved experimentally that the stomach has a chemical action on foods. Beaumont added greatly to our present day knowledge of Gastroenterology by his investigations of the digestion of foods and the action of gastric juice on them. Prout discovered that gastric acidity is due to hydrochloric acid. For a number of years thereafter, research in Gastroenterology was in a dormant state, until Kussmaul introduced the use of the stomach tube for the relief of a patient suffering with pyloric obstruction and gastric stagnation. Since Kussmaul's report in 1869, interest in the subject began to grow, and he may be properly recognized as the father of Gastroenterology. Physick and others, perhaps, had used stomach pumps before, but Kussmaul stimulated a real interest in its possibilities and usefulness. Subsequently, von Leube made use of the stomach tube for diagnostic purposes; he was the first to attempt a test meal; and he originated the term "nervous dyspepsia." Later, Oser used the first flexible tube. This was made workable by Ewald, who with Boas devised the expression method. Ewald and Boas followed with the use of the first practicable test meal; and they made serious attempts to study the action of gastric digestion. In 1886, Boas devoted himself to gastroenteric diseases. He was the first in Berlin (and probably in Germany) to open a clinic, and to give lectures on the subject. During the twenty years of his clinic, he devised the resorcinol test; defined acid gastritis; with his student Oppler, he drew attention to the Boas-Oppler bacillus in carcinoma, as well as to the importance of lactic acid in the same condition. He advanced the test supper to estimate motility; he demonstrated the incidence of 95 per cent of bleeding in carcinoma and its relative infrequency in ulcer, as well as a number of other important facts. Boas may rightfully be designated as the first gastroenterologist and teacher of the subject.

Outstanding contributions made by workers who were not gastroenterologists added to the growth of knowledge. Pavlov, Bayliss and Starling were notable in this connection, their work supplementing Beaumont's researches in physiology. One after another, significant observations were contributed. Some of these were as follows: Alvarez on rhythm studies of the digestive tract; Mann and van den Berg on the liver; Opie, Naunyn, Fitz and Minkowski on the pancreas; Funk, Mendel and Rehfuss on food responses; Runeberg on gastric and intestinal inflation; Einhorn on gastrodiaphany; Winter and Hayem on secretion and pathology (also, Cruveilhier on ulcer); Fenwick on gastric atony Reichmann on gastrosucorrhea chronica; Meltzer and Kronecker on deglutition sounds; Mikulicz, Rosenheim, Schindler and Jackson on gastroscopy; Roentgen, the discoverer of the X-ray, made practicable by Ridel, who first used opaque substances, further elaborated upon by Holzknecht, Haudeck, Cole, Cannon, Stewart, Forssell, Graham, S. Weiss, and others; Einhorn on the rice meal, and H. Strauss on the raisins and prunes to diagnose delayed gastric emptying; Ehrenreich in 1912 and Rehfuss in 1914, on fractional test meals; Schreiber and Reichmann on examinations of the contents of the empty stomach; Kelling on lactic acid tests; Munson, Chandler, Stiles and Kofoid on parasitology; von Leyden and von Noorden on nutrition; Boas, Boldyrev, Volhard, Einhorn, McClure and Bassler on pancreatic tests and methods; the urobilen, indican and uroresin tests, and Rosenbach on combined reactions; Ewald, Boas, Einhorn, and Dieulafoy on gastric pathologies; A Schmidt, Strasburger, and Bassler on test meals to examine intestinal conditions and methods; Cruveilhier, von Leube, Lenhartz, Einhorn, Sippy and others on the medical treatment of gastroduodenal ulcers, and Riegel on the use of alkalies; Einhorn (1909) on the duodenal tube for diagnosis and feedings; Meltzer and Lyon on biliary aspirations for diagnosis and treatment; Glenard on Splanchnoptosis and mechanical supports; Lockwood and Bassler on bed treatment for ptosis and other digestive states; Meltzer on his studies of dilations of the esophagus, and Plummer, Einhorn, and Crump on stretching methods;

*Several requests have been made to Dr Anthony Bassler, New York City, to reprint his article, "The History of Gastroenterology, published in the Review of Gastroenterology, March, 1934. In this article is an accurate account of men and events, especially those pertaining to the establishment of the Section on Gastroenterology and Proctology of the American Medical Association. In the historical reports made during the time of the Centennial meeting of the A.M.A. at Atlantic City, three organizations reported on this momentous occurrence of Gastroenterology and Proctology, two of them so erroneously that the record up to 1934 should be straightened out. —Editor.

Riegel on hyperacidity, Einhorn on achylia, Hemmeter on heterochylia, and Martius and Lubarsch on studies of anacidities; Herter, A. Schmidt, Castellani, Escherich, Distaso, Tissier, Eberth, Shiga, Flexner, Chalmers and Bassler on the bacteriology of the intestinal canal; Vincent on bacteriology of the mouth; and others, too numerous to mention, who have engaged in experiments which have served to fill in these investigations.

We should supplement this list of men and their work by some record of the remarkable advances made by surgeons in this field. Following Billroth, who did the first operation on the stomach, we should mention Woelfler and the Mayos on gastroenterostomy, and the contributions made by S. J. Weir, McBurney, Sands, Finney, Deaver, Murphy, Erdmann, Berg, and many others. While these men were primarily surgeons, they enhanced the practicability of the medical work by curative measures, elaborating means of study, etc.

With this rapid development (for, with exceptions, these advances have all been made in the last sixty years,) there was also a concomitant progress in the literature of the subject. Innumerable monographs describing definite entities and methods of diagnosis and treatment appeared. Following the initial text books of Ewald and then of Boas, as well as others in Europe and Great Britain, there were published in this country works by Einhorn, Hemmeter, Aaron, Stockton, Kemp, Bassler, Niles, Reed, Lockwood, Lyon, Rehfuss, Crohn, Kellogg, etc. The first periodical on the subject (in publication since 1890) originated at the suggestion of Boas, and was followed by others in France, Italy, South America and Japan. A similar attempt was made in this country about twenty years ago, which proved unsuccessful.

A national society, the American Gastroenterological Association, the first of its kind to be organized, was formed in the United States in 1897. In 1914, Germany followed suit. Credit must be given to Aaron of Detroit for his organizational efforts in the establishment of the American society; Boas is largely responsible for the German society. Stockton was president, Einhorn vice-president, and Aaron secretary of the former. Ewald, Boas, and von Noorden were the first three presidents of the society in Germany. Both societies permitted surgeons to become members.

Undoubtedly the most prominent organizational event in Gastroenterology was the establishment of the Section on Gastroenterology and Proctology in the American Medical Association, the first meeting of which was held in 1917. Its establishment necessitated a five years' battle against the most rigid opposition. When finally formed, it legalized so to speak the specialty of Gastroenterology, and was supported by the largest medical organization in the world. Prior to this, there had been much opposition, both from the internists and surgeons, but this has disappeared. This Section proved a stimulus to higher standards of work, and the investigative results were promptly disseminated among the profession in this country. The first officers of this Section were Murray, president; Bassler, vice-president; and Hirschmann, secretary. In the second year, Bassler was president; Graham, vice-president, and Soper, secretary. Subsequently, the Southern Gastroenterological Association was formed, which finally was incorporated in a newly organized Section on Gastroenterology in the Southern Medical Association. Since that time, there have been a number of local organizations, notably the one in New York City which at times meets jointly with the New York Academy of Medicine, and the recently established organization under whose auspices this publication is issued, the Society for the Advancement of Gastroenterology of which Manning is president.

While these various activities were taking place in the United States, the subject was taught in several institutions. There were several full professorships established in Gastroenterology. In New York City, Einhorn began lecturing (1888) on Gastroenterology, at the New York Post Graduate Medical School and Hospital, with the rank of Professor of Gastroenterology. At the New York Polyclinic, where a department in the subject has been maintained for many years, the Professors in Gastroenterology, were Nesbitt, Hayes, Kellogg, Bassler, Manning, Cash, Weiss, assisted by other well known workers in the field. The first undergraduate medical school which established a full professorship in New York City was Fordham University, Kemp being the first professor. He was succeeded by Bassler, who also occupied the same position at the New York Polyclinic. In the Homeopathic College, Upham is professor. At New York University and Bellevue Medical College, Mills Sturtevant presides over the department; in the College of Physicians and Surgeons, Kantor and Crump, and Crohn at Mt. Sinai are in charge. In the Long Island Medical College, Andresen is head of the department, and Chace and Kast have charge of the subject in the Post Graduate Medical School. Various other professors and teachers in the United States have become widely known: example, Aaron in Detroit; Jones and Aaron in Buffalo; Smithies, Carlson and Portis in Chicago; Rehfuss, Bockus, Eberhart and Lyon in Philadelphia; White in Boston; Simon in New Orleans; Alvarez and Eusterman in the Mayo Clinic; Harris in Birmingham; Morgan and Verbryeke in Washington; Soper in St. Louis; and others.

Those who read this very brief and fragmentary sketch may grasp some idea of the history and the field of interest in Gastroenterology. While the subject is an integral part of internal medicine, the specialists in this branch have given to internal medicine an elaboration of the subject which could not have been made by the general internist alone. Most of the advances in the clinical and laboratory phases have come from men who have devoted their interests, for the most part, to the medical abdominal field. It is now time for those workers who are especially interested in this branch of medicine to organize Sections in Gastroenterology in medical institutions, colleges, hospitals, and clinics.

No specialty has a more elaborate background than Gastroenterology, and none has had more intense and zealous workers. They have spread their work and knowledge to help the entire profession, and they have

exhibited an untiring energy in the process. Theirs is surely a glorious record of achievement. With such a heritage, we can do no less than to carry on their work and to elevate the study and practice of Gastroenterology to the position of importance in the medical field it deserves.

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ANTIBIOTIC-PRODUCING COLIFORM ORGANISMS IN THE INTESTINES

Halbert and Gravatt reported in the last issue of the Public Health Reports (64: 313-318, 1949) another series of their observations on antibiotic-producing organisms in the stools. The beginning of the search for such organisms dates back to the publication of Gratia in 1925 who found antagonism between E. coli strains in vitro. Before the penicillin era, such phenomena were suspected of being the results of bacteriophage action. During recent years, Gratia, Fredericq and Halbert established true antibiotic action exerted by several bacterial strains belonging to the coliform group and isolated from the feces. Active antibiotics, however, are not being excreted in the stools. It is possible that such substances are destroyed before the feces are passed. Halbert and Gravatt hope that examination of the contents of the large bowel will shed light on this question.

Microbial competition presents a considerably complicated problem from the point of view of the enteric microbiologist. A cursory glance through the literature shows that we still lack the basic knowledge of the "normal" intestinal flora and fauna. The methods we are employing for the detection of pathogenic microorganisms preclude the study of so-called non-pathogenic organisms, especially if, in an attempt to achieve greater efficacy, we streak more and more selective and inhibitory plates. Little or no attention is being paid to intestinal molds and yeasts. Even if we attempt to penetrate into the realm of "coliforms", we seldom go beyond their rough grouping according to the IMVIC reactions. Reports on the "normal" bacterial flora, especially in children, are contradictory and rarely enlightening. Thus our lack of knowledge of microbial interrelationships roots deeply in our deficiency to be able to build on the understanding of microbes normally present in the intestines. This holds true not only for gram negative bacteria but also for cocci and gram positive rods.

The existence of microbial antagonism has been known for a long time, even before its actions were expressed in proper words by d'Herelle and by those who did the fundamental work on penicillin. Bacteriologists have always wondered about their difficulties in obtaining postive stool cultures, especially in certain phases of shigellosis. While the addition of 1:10,000 formalin, according to Kligler et al., checks bacteriophages in the feces and leads to a higher number of positive cultures, no general routine method is known for the prevention of antibiotic activity, especially in the higher parts of the bowel. Thus the diagnostic bacteriologist is still very much concerned with antibiotic-producing organisms which may influence his results. The clinician, on the other hand, would be most anxious to be able to lay his hands on an antibiotic-producing inhabitant of the normal intestine and use it in the treatment of enteric infections.

With the advent of hyaluronidase, something new was added to the already complex problem of microbial interaction. Many continental workers insist that Endamoeba histolytica is unable to penetrate the intestinal mucosa if bacteria do not prepare the path for it. Some experimentators tried to find out if hyaluronidase is being produced by E. histolytica. Such an enzyme would enable this protozoan to penetrate into the tissues. The results of in vitro experiments, however, were conflicting. A theory was emulgated recently saying that sporeforming anerobic grampositive rods which often produce hyaluronidase, facilitate the attack of E. histolytica on the intestinal mucosa. The role of hyaluronidase has not been established as yet in bacterial action in the intestines.

Synergism among bacteria, mycotic elements and protozoa has not been studied as yet to a satisfactory degree with regard to the intestines, while much information is already available on similiar problems in wound infections. Again, the lack of knowledge of the "normal" flora turns any attempt to clarify this problem into staggering in the dark.

Exotoxin production (as by Shigella dysenteriae Shiga), liberation of endotoxins (as by some Salmonellae), the presence of hyaluronidase-like (but not identical) substances (as in Vibrio cholerae), sensitization by absorbed "toxic" products (as in amebiasis) help to complicate our task in finding the answers to many of our questions. And, if we are considering antimicrobial actions, let us not forget the problem of coproantibodies which have also been recently studied in this country. The methods used for the detection of these antibodies are quite cumbersome. Let me add frankly, that our own technic, which is a modification of Weil's method for the evaluation of protective antibodies against Enterobacteriaceae using developing chick embryos has brought us much disillusionment. Great difficulties are encountered if one tries to evaluate agglutinating, precipitating and complement fixing antibodies in the stools. It seems that before antibodies can be studied further, much experimental work concerning methodology has to be performed.

Finally, we have to face the question of simple absorption. Are viruses absorbed by bacteria and by other elements in the intestines? Are bacteria and mycotic elements devoured by protoza or do they actively attack amebas and flagellates under certain conditions?

Thus the problem of the great world inside every individual's intestines becomes more and more involved. The work of Halbert and his associates deserves much attention and should be merited as a step toward an ultimate solution.

DR. OSCAR FELSENFELD, CHICAGO

Volume 1
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General Abstracts Of Current Literature

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CLINICAL MEDICINE

MOUTH & ESOPHAGUS

SCHOLEFIELD, J.: *Spontaneous perforation of the esophagus: surgical repair, with recovery.* (Brit. Med. J., Feb. 26, 1949, 348-350).

Only 60 cases of spontaneous rupture of the esophagus appear in the world literature, and in 3 cases, one of which is described, recovery took place as a result of surgical intervention. The mortality without surgery has been practically 100 per cent, the patient dying within 48 hours. The tear is usually one inch long, in the lower end of esophagus and is due always to increased intra-thoracic pressure during severe vomiting. Extravasated food material and gastric juice produce mediastinitis and pleural effusion. Surgical emphysema begins over the sternum and may involve the whole upper trunk and head. Pain is extremely severe, located substernally or in the epigastrium and radiating to the back. Shock is present. Mistaken diagnosis of perforated peptic ulcer, coronary occlusion, dissecting aneurysm of the aorta, acute pancreatitis, acute cholecystitis and spontaneous penumothorax have been made but should be prevented by the appearance of subcutaneous emphysema. *Morphine has little effect on the pain.* In the case successfully treated, a transthoracic approach was employed, and antibiotics and intravenous plasma transfusions were liberally used.

CROSS, W. G.: *Oral reactions to pencillin.* (Brit. Med. J., Jan. 29, 1949, 171-173)

Glossitis, black tongue and stomatitis may occur as a result of oral reactions to locally used penicillin wafers. These, and other observed reactions, were due to the penicillin itself. The reactions do not occur until there has been a complete change in the character of the oral flora, which requires about 48 hours, and it seems reasonable to limit the use of penicillin for the treatment of oral infections to this length of time, as a rule. To maintain an adequate and continuous concentration of penicillin in the mouth, the use of this antibiotic in chewing gum, 10,000 units per piece, thrice daily, is suggested.

DOSCHERHOLMEN, A.: *Gas gangrene from alveolar periostitis.* (Nordisk Med., Dec. 24, 1948, Vol. 40, No. 52, 2421-2422).

A man, 19 years of age, developed severe cellulitis of the neck from an alveolar periostitis. In spite of surgical treatment and penicillin and sulfathiazol medication, the following complications occurred: Dry pleurisy of the right side, dry pericarditis, and empyema of the left plexra, from which only strictly anerobic gram-positive bacilli were cultivated. The empyema was subjected to surgical and penicillin treatment. Nine days following complete recovery the patient returned suffering from acute epididymitis probably metastatic, the bacteriological etiology of which could not be ascertained. A second penicillin-sulfathiazol course cured him entirely.

STOMACH

PALMER, E. D.: *The proper use of the gastroscopic method.* (Bull, U. S. Army Med. Dept., March, 1949, Vol. IX, No. 3, 207-211).

Inasmuch as the clinical diagnosis of intragastric organic disease is difficult from the standpoint of symptoms and physical findings, and since X-ray reports frequently are negative when the internist may suspect actual lesions of being present, the resort to gastroscopy should be made before the ailment under consideration be viewed as functional and relegated to the psychosomatic classification. Gastroscopy must always be considered as a procedure supplementary to other methods of examination and cannot be regarded as a panacea in diagnosis, although it alone gives us a satisfactory knowledge of the condition of the gastric mucosa. The diagnosis of gastritis depends entirely upon gastroscopic examination, and frequently functional dyspepsias are really caused by chronic gastritis. Gastroscopy is less unpleasant than gastric analysis. The most frequent hazard is a severe reaction to the pontocaine used as a throat anesthetic, and occurs once in 500 examinations on persons who have been given pre-examination barbiturate, and once in 100 where the barbiturate has been omitted. Mechanically, the instrumentation is safe and shows a mortality of only 0.004 per cent. The training of the gastroscopist is a difficult one and due experience in technique and interpretation of findings can only come during a large post-graduate experience.

MISCELLANEOUS

DOHL, F.: *Paralysis of the diaphragm.* (Nordisk Med., Sept. 3, 1948, Vol. 39, No. 36, 1608-1611).

The author states that acute paralysis of the diaphragm will often give a well-defined syndrome,—inspiratory pains, reduced movements of the affected side of the chest, inspiratory bulging of the intercostal spaces and pains in the upper abdominal quadrant and in the shoulder. This syndrome is characteristic not only of primary phrenic myositis but also of diaphragmatic palsy due to pulmonary tuberculosis, exudative pleurisy and cancer of the lung.

Evaluation of Clinical Methods in Gastro-Intestinal Disease.

II. Cholesterol Determinations in Peptic Ulcer

By

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and

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The necessity for determining the cholesterol level in a patient with gall bladder disease is widely accepted. The value of this determination in other gastro-intestinal diseases, such as peptic ulcer, however, is still open to wide differences of opinion. As part of a study[1] in evaluation of modern methods of diagnosing gastro-intestinal disease, it was felt worth while to examine more closely the role played by cholesterol in peptic ulcer.

As far back as 1927 Jarno[2] claimed that there is a hypercholesterolemia in peptic ulcer and believed he could relieve the ulcer symptoms simply by increasing the blood cholesterol by diet. He further maintained that in various conditions having a low gastric acidity there was an elevated cholesterol—i.e., that cholesterol varied inversely with gastric acidity. More recently Hyman[3] revived interest in the possible relationship of cholesterol to peptic ulcer by asserting that "gastric acidity, secretion and motility may be influenced by the level of blood cholesterol." He suggested that "peptic ulcer may be treated through a prolonged elevation of blood cholesterol by adding large amounts of lecithin and cholesterol to the diet." He states that in peptic ulcer there appears to be an inverse relationship between blood cholesterol and peptic secretions, and a direct relationship between blood glucose and cholesterol. Since these relationships form the basis for his concept of the beneficial effect of cholesterol in peptic ulcer it was considered worthwhile to investigate them. We therefore, determined the free and total acidity, the blood glucose and cholesterol levels in a number (35) of peptic ulcer cases and compared the findings with an equal number of "functional" gastric cases.

METHODS AND FINDINGS

With our study in view a cholesterol determination by the Leiboff Method[4] (normal is 140-180) was made on all gastro-intestinal cases receiving complete work-up in our office and hospital practice during 1947 and in the spring of 1948. The complete work-up included the determinations which concerned us in this study—cholesterol, blood sugar (Folin and Wu method, normal is 80-120) and gastric analysis (free and total acid after Ewald meal). Thirty-five consecutive patients who had peptic ulcer (both clinically and roentgenologically) were selected and compared with 35 consecutive functional gastric patients (29 functional dsypepsias and 6

CASE	Ewald Meal FREE	Ewald Meal TOTAL	GLUCOSE	CHOLESTEROL
PEPTIC ULCERS-MALE				
1	15	31	94	200
2	16	33	103	189
3	20	38	115	181
4	18	30	80	180
5	45	66	98	163
6	35	52	85	202
7	52	94	93	163
8	48	82	100	178
9	34	48	90	164
10	34	49	100	193
11	30	48	116	190
12	13	24	85	163
13	18	34	82	193
14	12	22	90	183
15	32	55	96	166
16	38	58	130	174
17	36	53	90	186
18	37	59	85	180
19	46	62	86	173
20	48	69	99	182
21	40	69	87	186
22	38	70	93	178
23	40	76	107	196
24	36	54	166	212
25	40	72	125	192
26	38	58	105	195
27	40	64	95	196
28	35	60	80	172
29	30	46	104	179
30	40	70	112	172
31	25	36	74	198
Average of males	33.2	54.2	98.9	183.9
PEPTIC ULCERS-FEMALE				
32	20	34	80	147
33	15	35	95	198
34	28	50	84	178
35	35	72	89	204
Average of females	24.5	47.8	87.	181.8
TOTAL AVERAGE	32.2	53.5	97.5	183.6

From the Medical Service of the New York Medical College Flower and Fifth Avenue Hospital (Metropolitan Hospital Division).

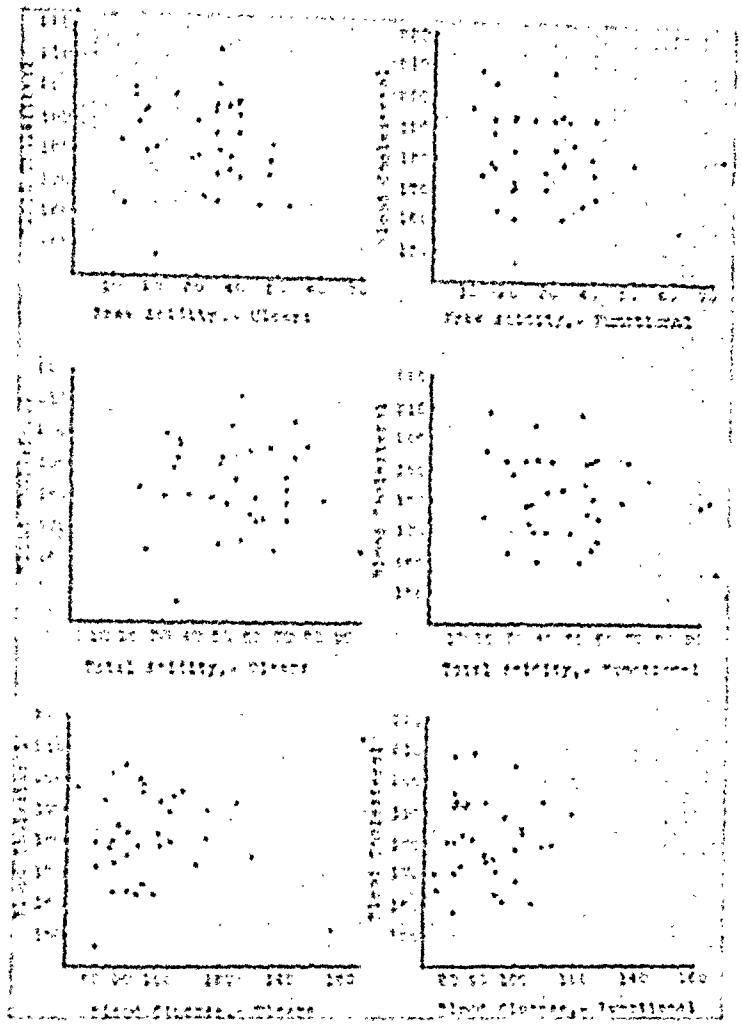


Fig 1. The gastric acidity, blood glucose and blood cholesterol in 35 consecutive cases of peptic ulcer compared with 35 unselected cases of functional gastric disorders.

CASE	Ewald Meal FREE	Ewald Meal TOTAL	GLUCOSE	CHOLESTEROL
FUNCTIONAL DISEASE-MALE				
1	62	96	89	152
2	34	52	85	192
3	40	56	92	174
4	20	38	82	192
5	12	20	80	208
6	15	24	92	188
7	32	55	81	193
8	45	95	112	178
9	20	33	82	172
10	33	92	80	190
Average of males	35.8	56.1	87.7	192.4
FUNCTIONAL DISEASE-FEMALE				
11	20	36	109	193
12	15	25	84	192
13	40	56	100	167
14	14	32	100	178
15	20	31	80	192
16	37	54	74	164
17	28	52	90	176
18	20	34	80	170
19	15	30	109	175
20	35	52	102	184
21	25	40	115	192
22	28	64	76	150
23	25	46	73	170
24	32	54	86	181
25	20	36	96	160
26	30	54	83	192
27	20	50	86	208
28	10	18	80	196
29	16	26	93	163
30	40	66	82	182
31	30	44	102	183
32	20	35	94	170
33	32	50	105	160
34	15	35	100	204
35	12	18	90	174
Average of females	24.9	41.6	88.2	180.8
TOTAL AVERAGE	25.2	45.8	88.1	181.2

Table 1. The free and total gastric acidity, blood glucose and cholesterol in 35 patients with duodenal ulcer as compared with 35 consecutive "functional" gastric patients.

ptoses). The cholesterol, glucose and gastric acidity findings in these cases were compiled in Table I and charted graphically in Fig. I, so as to lend itself more easily to statistical analysis. Review of the data from the statistical point of view establishes the fact that there is no statistical correlation between gastric acidity and cholesterol in either ulcer or the functonal gastric cases. There is furthermore no correlation between the blood glucose and cholesterol levels in either ulcer or functional cases.

It is to be noted that in the ulcer group there are 31 males and only 4 females, whereas in the functional groups the preponderance is reversed, 25 females to 10 males. It may be argued that the two groups are not strictly comparable since one is largely male, the other largely female, and there is supposed to be a distinct difference in the cholesterol level of male and female. Our data however does not show any appreciable difference due to sex. Within the functional group the average cholesterol figure for the male is 182,—essentially the same as for the female (181). The same is true of the cholesterol figures in the peptic ulcer group,—the average is 184 for males and 182 for females. It was therefore considered satisfactory to compare the cholesterol, glucose and acidity findings in the ulcer cases with the findings in the functional cases. The results do not corroborate the basis for the proposal of high cholesterol diets in peptic ulcer, for they show no constant relationship of cholesterol to either gastric acidity or to blood glucose. There is futhermore accumulating evidence that hypercholesterolemia is etiologically related to arteriosclerosis and atherosclerosis.[5,6]. In face of such evidence it appears inadvisable to attempt to produce hypercholesterolemia in any patient. It is felt that cholesterol is not closely enough related to gastrointestinal disease to warrant its routine determination in cases other than gall bladder disease.

SUMMARY

A study to determine the possible relationship of cholesterol to peptic ulcer was made comparing the findings in 35 proven cases of peptic ulcer with 35 functional gastric cases.

No relationship between cholesterol levels and gastric acidity or blood glucose was found either in the ulcer or the functional cases. This lack of correlation, as well as the growing evidence for the causal relationship of cholesterol to arteriosclerosis and atherosclerosis speak against the use of high cholesterol diets in the treatment of peptic ulcer.

There appears to be no valid reason at present to routinely determine the cholesterol level in the study of a patient with peptic ulcer. Its usefulness is largely limited to gall bladder investigations.

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We are deeply indebted to Miss Claire Lingg, Chief Statistician of the New York Heart Association, for the statistical review of the data presented in this study.

Experiences with Sodium Carboxymethylcellulose as an Antacid

By

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INTRODUCTION

OUR EXPERIENCE WITH THE PREPARATION OF sodium carboxymethylcellulose in tablet and liquid form extends from February, 1948 to the present, December 15, 1948. Obviously, in this short period of time, conclusions as to the long term effects on such a chronic recurrent disease as peptic ulcer of the stomach and duodenum cannot be made. However, observations made during this period are recorded from a small series of patients. Tablets containing 450 mgm. of sodium carboxymethylcellulose and 150 mgm. of magnesium oxide (hereinafter called SCMC) and a 5% liquid preparation of sodium carboxymethylcellulose were used in varying dosages to be outlined.*

The difficulties in evaluating any type of therapy in the treatment of duodenal ulcer have been recently stated by Sandweiss, Sugarman, and Lockwood[1]. In their report, enterogastrone is found to be disappointing when used as the only mode of therapy. More pertinent to the present report is the comparison of enterogastrone by the authors with several other methods of therapy. It seems useful to reproduce this data in the form of the table which appears in the authors' article. (Table 1.)

It is of interest to note that even parenteral distilled water as a form of treatment will induce improvement

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* This preparation is marketed under the trade name of CARMETHOSE, and was furnished by Ciba Pharmaceutical products, Inc., Summit, N. J.

Table 2

RESULTS OF USE OF SCMC IN PATIENTS WITH DUODENAL ULCER

Case	Color-Sex	Age (yrs.)	History	Follow-up (mo.)	Results
1	W.M.	43	5 years	5 months	good
2	W.M.	47	15 years	4 months	good
3	C.M.	37	2 years	6 months	good
4	C.M.	58	6 years	5 months	good
5	W.M.	62	4 years	6 months	good
6	W.F.	39	19 years	6 months	good
7	C.F.	28	2 years	4 months	good
8	C.M.	62	10 years	4 months	good
9	W.F.	26	1 year	3 months	good
10	W.M.	32	3 years	4 months	good
11	W.F.	44	6 years	4 months	good
12	W.M.	38	7 years	5 months	good
13	W.M.	31	3 years	3 months	good
14	C.F.	38	4 years	3 months	good
15	W.M.	32	4 years	4 months	good
16	W.M.	46	10 years	4 months	good
17	C.M.	38	4 years	5 months	good
18	W.M.	56	8 years	4 months	good
19	W.F.	44	5 years	5 months	good
20	W.M.	26	2 years	3 months	good
21	W.M.	24	1/2 year	2 months	good
22	W.F.	52	12 years	3 months	good
23	W.M.	26	2 years	2 months	no change
24	C.M.	60	7 years	3 months	no change
25	W.M.	22	3 years	2 months	no change
26	W.M.	27	3/4 year	2 months	no change
27	W.F.	58	2 years	2 months	feels worse
28	W.M.	23	1 1/2 year	2 months	feels worse

seen at least every two weeks, but most were seen weekly. The hospitalized patients were seen daily. Only enough of the medication to last through the interval between clinic visits was supplied.

Dosage was varied and will be discussed separately. However, when a plan of dosage was started, it was maintained throughout, with certain exceptions. Excessive doses of the liquid preparation were purposely given to determine whether any toxicity would ensue.

As previous studies of the effect of SCMC on gastric acidity had been made[4] and since clinical correlations of these results in human patients are generally not absolute, we depended primarily on the subjective findings to evaluate the effectiveness of SCMC. Experience also indicates that correlation of clinical results with X-ray findings are also not absolute. However, all of these patients had at least one upper gastrointestinal radiologic study to confirm the diagnosis in each case.

RESULTS

Table 2 is a summary of the clinical results. Twenty-two of the patients had better relief with the use of SCMC than had been previously experienced with other antacids or alkalis. In four patients there was no improvement and two stated that they felt worse. In no case was *constipation* a complaint, which is a marked advantage, as twenty-four had been constipated at one time or another during previous ulcer therapy. This was particularly true of sixteen patients who had used aluminum hydroxide preparations. In these individuals constipation usually necessitated the use of laxatives at more or less regular intervals. In no patients taking either tablet or liquid SCMC were laxatives necessary. Even in those whose ulcer symptoms did not improve, complaints of constipation were not offered.

On the whole then, it appears that SCMC is as satisfactory an antacid as others in common use, if not superior. Its greatest advantage seems to lie in its anti-constipation effect in a group which uses laxatives commonly. With its satisfactory antacid effect and laxative action, SCMC would appear to have superiority over most of the current antacids and alkalis since these are, on the whole, constipating. This is especially true in the elderly patient, in whom the occurrence of fecal impaction and its sequelae occur not uncommonly, especially when aluminum hydroxide preparations are used.

SPECIAL STUDIES AND OBSERVATIONS

In five patients special gastroscopic studies were done. In three of these, the X-ray studies were negative for gastric or duodenal pathology while two patients had an X-ray diagnosis of duodenal ulcer. In all cases, the following routine was followed: Nothing by mouth for at least eighteen hours, preparation with 15 mgms. morphine, 0.5 mgms. of atropine sulfate, and gargle with pontocaine.

However, in these five cases an addition was made. In two cases, one tablet of SCMC was taken orally two hours before gastroscopy; in two other cases one tablet of SCMC was taken one hour prior to gastroscopy and in one patient two tablets of SCMC were given two hours prior to gastroscopy.

In four of these cases, gastroscopy proceeded without incident. In these four cases, including the patient given two tablets of SCMC, gastroscopy revealed that there were no large undissolved particles present. It was felt that the rather large white SCMC tablets were not present in whole or in part. There was noted a rather glairy mucoid-like covering over all parts of the observed stomach. This rather obscured the usually well seen mucosal detail. Our conclusion was that in these cases, one SCMC tablet will dissolve in the fasting stomach within two hours. This was also true of the two tablets in the one case observed.

In one of the patients who had taken one tablet two hours prior to gastroscopy, introduction of the gastroscope into the stomach proceeded without incident. However, nothing could be seen and after five minutes the gastroscope was withdrawn. Sticking tightly to the mirror at the end of the gastroscope, and completely covering it, was the tablet of SCMC. It was about half the original size. It was felt that the adherence to the mirror occurred as the gastroscope was being passed through the esophagus. This was really not very remarkable because these patients had swallowed one or two tablets without the aid of water, since gastroscopy was to be done. The remarkable thing, in retrospect, is that the other patients did not have the difficulty with the tablet sticking in the esophagus, under these circumstances: no concurrent administration of water. This experience should not have been unexpected in

being considered.

It is our impression that liquid SCMC acts more promptly than the tablet form. In the acute cases, it was deemed preferable. It is our antacid of choice in bleeding ulcer patients. It is more palatable than the other liquid antacid preparations and may be used in conjunction with the tablet form. The tablet form has wider applicability since it can be carried easily. In severe acute attacks, however, the liquid form appears to be better, while for maintenance the tablet form is equally good.

SUMMARY

1. Twenty-two of twenty-eight patients with duodenal ulcer obtained satisfactory clinical results with the use of sodium carboxymethylcellulose.
2. The liquid form acted more quickly than the tablet form which was equally satisfactory for maintenance.
3. In bleeding peptic ulcer, the liquid form is preferable.
4. Gastroscopy shows the tablets to be dissolved in the stomach within one to two hours.
5. Excessive doses were given, but no toxic or side reactions were noted.
6. Constipation was not present in patients taking this drug. SCMC acts as a mild hydrophilic bulk laxative.
7. SCMC appears to be just as satisfactory as currently used antacids and eliminates the usual constipating action of others, especially aluminum hydroxide preparations.

SUPPLEMENTAL REPORT

Since submission of this manuscript, the follow-up has been extended seven months, so that the longest period of follow-up is now fourteen months in the patients presented. The patients have maintained their improvement while on the drug and followed in the clinic. There have been three recurrences in the patients who stopped using the drug. These three patients have returned and are again getting relief of their symptoms with the drug.

Additionally, twenty more patients are taking the preparation, either by liquid or tablet form, with similar results to the cases herein reported. In all cases, a striking feature has been the absence of constipation and the avoidance, in many instances, of additional laxatives, which were used frequently when other antacids were taken.

In the past 6 months, a smaller tablet, containing 125 mgm. sodium carboxymethylcellulose and 75 mgm. magnesium oxide, has been used. The difficulty in swallowing mentioned in this paper, has not occurred with the smaller tablets which is the size available commercially (Carmethose).

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Carboxymethylcellulose as a Colloid Laxative

By

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The effect of sodium carboxymethylcellulose as a hydrophilic colloid laxative was studied in 250 patients during a three-year period. We were anxious to give this synthetic cellulose gum a thorough clinical trial in spite of the fact that there are so many cathartics already available, since it gave promise of possessing important advantages over any of the others. Our clinical impressions and other observations are summarized below:

1. Sodium carboxymethylcellulose is an effective colloid laxative and is apparently completely non-toxic.
2. Since it produces no roughage to irritate delicate mucous membranes of the gastro-intestinal tract, it is of particular value in patients with irritable or spastic bowels and can be used advantageously in cases of hemorrhoids and proctitis.
3. This synthetic cellulose gum has a marked lubricating property which facilitates defecation. This property may well account for the fact that it produces satisfactory results in much smaller dosage than is necessary with other colloid laxatives.
4. Sodium carboxymethylcellulose is tasteless, odorless and non-toxic. It does not interfere with the absorption of essential nutritional elements, nor does it absorb fat soluble vitamins from the intestinal tract.
5. None of the patients in our series developed intestinal impaction, even though the gum was administered to some patients for many months.
6. In cases of diarrhea, sodium carboxymethylcellulose has an apparent ability to absorb irritating toxins

* The carboxymethylcellulose used in this study was supplied by the National Drug Company, Phila., Pa.

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from the intestinal tract, and tends to produce normal stools.

The gum was first obtainable only in powder and granule form. It is now available in a much more convenient tablet form.* It appears to be equally effective in this form, and is, of course, easier for patients to swallow.

Toxicity, Sensitivity and other Studies: Brown and Houghton[1] and Werle[2] found sodium carboxymethylcellulose to be non-toxic when fed in large amounts to animals. Young rats maintained by Rowe et al[3] for a period of eight months on diets containing five per cent by weight of sodium carboxymethylcellulose, equivalent to the ingestion of two to three grams per kilo of body weight per day, manifested no ill effects. Another group of nearly mature female rats were maintained for two months on diets containing twenty per cent by weight of sodium carboxymethylcellulose, equivalent to eleven to thirteen grams per kilo of body weight per day, without the production of any deleterious effects upon organ weights or on histopathological examination. The feces were observed to be softer. A slight growth curve depression, of questionable significance, was noted, this can be explained by the increase in the bulk of the diet to the exclusion of nutrient food.

A comparative study, to determine the acute oral toxicity values in white rats and guinea pigs of sodium carboxymethylcellulose, locust bean gum, edible gelatin, karaya gum, citrus pectin and gum tragacanth, was made by Shelanski and Clark[4]. The results indicated they were all in the same range of toxicity. Daily feedings of one gram of sodium carboxymethylcellulose per kilogram of body weight to white rats for a period of twenty-five months produced no deviation from the control group in regard to fertility, blood counts, urinalysis, weight change, gross and microscopic pathological examination of heart, liver, stomach, intestines, kidneys, spleen and adrenal glands. Approximately 90% of the sodium carboxymethylcellulose fed to the rats was reclaimed in the feces.

It was demonstrated by means of patch tests in two hundred human subjects that sodium carboxymethylcellulose is neither a primary skin irritant nor a sensitizing substance. Five grams of the compound mixed with an antiseptic substance were used in 134 cases of vaginal infection without any evidence of irritation of the vaginal mucosa or external genitalia[4].

No significant mucosal irritation could be detected in 22 patients who were taking 6 to 18 grams of the colloid laxative daily for a period of six months and subjected to monthly sigmoidoscopic examinations.

Procedure of Treatment and Results: In starting the average patient on any colloid laxative, he should be made aware of the difference in action of this type of laxative as compared to stronger and harsher laxative preparations. If the patient is the least bit apprehensive about missing a bowel movement or is extremely constipated, his previous laxative should be used in reduced amounts in conjunction with the colloid laxative and gradually decreased until eliminated.

Sodium carboxymethylcellulose was used as a colloid laxative in 250 patients having various degrees of constipation; but in the majority no pronounced pathological disturbances of the gastro-intestinal tract were present. More than fifty per cent of these patients have taken this laxative for six to twelve months without any signs of ill effects or loss of laxative effect.

Initially, we gave from two to four grams morning and night with a full glass of water. Markedly constipated patients were given four to six grams three times daily, and were slowly weaned away from the harsh laxatives. After the first few months, we reduced the dosage in most patients by 50%, and have since come to the conclusion that the large doses we first tried are seldom necessary to produce satisfactory results.

In the vast majority of cases, 2 to 5 of the new 0.75 Gm. tablets in the morning and again at night have proved to be effective initial doses. After a few weeks most patients have experienced satisfactory bowel movements and normal stools with a dosage of 1 or 2 tablets 3 times daily.

In the average constipated patient normal bowel movements would occur in two to ten days with sodium carboxymethylcellulose. However, patients accustomed to harsh laxatives were slower in responding. Grouping of patients and results are given in Table I.

Of the 250 patients treated with sodium carboxymethylcellulose for constipation, only six patients failed to revert to normal bowel habits. Two of these patients had an aversion for jelly-like substances and could not swallow the preparation. Had the compressed tablets been available, these patients probably would have had no difficulty taking the preparation. Slight crampy pains were experienced by two patients who had an irritable bowel syndrome. This phenomenon may have been due to an increase in peristalsis or may have been coincidental with their usual pains. Two markedly constipated female patients apparently derived no therapeutic effect from as much as nine grams of sodium carboxymethylcellulose daily.

It was observed that the average constipated patients started to have normal daily bowel movements in one to three days; the patients with more chronic and marked constipation required larger doses of the laxative and an average of six to ten days to obtain the desired results.

DISCUSSION

The increased incidence of serious gastro-intestinal disturbance occurring in many patients today is no doubt due to the habitual use of harsh laxatives or cathartics to stimulate bowel movements. An occasional dose of a laxative or cathartic cannot be condemned, but a constant exposure of the gastro-intestinal tract to the abuse by a cathartic is deplorable and frequently leads to a habit which may result in serious organic disturbances.

TABLE I

NO. OF CASES	DEGREE OF CONSTIPATION	PREVIOUS LAXATIVE USED	DOSAGE OF CMC	RESULTING BOWEL ACTION	LAXATIVE EFFECT
15	Grade 1 Hard daily B.M.	None	2-3 grams nightly.	One daily B.M.—soft. Occas. two/day. No failures, except two couldn't swallow it.	1-2 days
19	Grade 2 Hard scybalous daily B. M. Will occas. miss.	Mild Lax. e.g. milk of mag. mineral oil	2-4 grams nightly.	One daily soft B. M. no failures	1-3 days
107	Grade 3 Hard B. M. every 1-2 days	Mod. strong laxatives	3-5 grams morn. & night	One daily soft B.M. Occas. two B.M. per day No failures	2-6 days
102	Grade 4 Hard B. M. every 2-3 days	Habitual strong laxative user	3-6 grams two or three times a day	One B.M. every one or two days. Two failures due to cramps causing discontinuance	4-10 days
7	Grade 5 No B.M. without laxatives	Strong laxative without effects. Enemas	6-8 grams three times a day	One B.M. every 1-3 days. One failure later had success. One complete failure.	2-4 wks.

The problems of constipation are varied and complex with many factors to be considered when dealing with this problem. The present day diet such as the "business men's or stenographer's lunch", consisting of foods with low fiber content and little or no roughage predisposes to constipation of a functional nature.

Probably the most important single factor is the patient's mental attitude. Oftimes the intestinal gradient is normally of a sluggish nature so that the individual does not have a bowel movement for several days. Although this may be normal for this individual it may cause him some concern leading to the use of strong laxatives, which may result in an irritable or spastic bowel. This type of patient can be helped by first allaying his concern about constipation; secondly, by the withdrawal of any irritating laxatives. During the period of readjustment, a colloid type of laxative, such as sodium carboxymethylcellulose, is of great value from the physiological and psychic points of view.

The physiological action of sodium carboxymethylcellulose to produce a safe and natural bowel movement is due to two characteristics of the compound. First, is the formation of a hydrophilic, undigestible gel which prevents the excessive absorption of water from the bowel and resultant hard feces. Second, is the lubricating qualities of this gel which aids in the passage of the feces. These factors account for the high laxative effect of small amounts of sodium carboxymethylcellulose. With daily soft stools, the psychic trauma produced by unfounded fear of constipation is eradicated. In cases of irritable or spastic bowels, the amount of sodium carboxymethylcellulose will be decreased when the bowel irritations and spasms have subsided. Patients with atonic constipation should be slowly weaned from their former laxative when started on sodium carboxymethylcellulose.

Sodium carboxymethylcellulose can be used advantageously in patients suffering from hemorrhoids and proctitis. The purpose is to produce a soft, lubricated stool, to minimize trauma to the pathological tissue of the anus during defecation. It has the advantage over mineral oil in that fat soluble irritants are not left clinging to the inflamed mucosa, there is no fear of leakage, nor does it absorb fat soluble vitamins from the intestinal tract.

Sodium carboxymethylcellulose may have practical therapeutic effect in diarrheas where the irritating toxins of the intestinal tract would probably be absorbed into the gel and the liquid stools would tend to become solidified; however, more studies will have to be conducted along these lines.

Contra indications to the use of sodium carboxymethylcellulose are suspected obstruction or any constricting lesions of the bowel.

SUMMARY

A new cellulose gum, sodium carboxymethylcellulose, is described which can be used advantageously in the successful treatment of a majority of chronic constipation cases.

Over 250 patients, with various degrees of constipation, picked at random from a general practice, were all markedly benefited by the use of small amounts of sodium carboxymethylcellulose. Five to ten tablets daily for the first few weeks, then one or two tablets

three times daily thereafter proved to be an effective dosage schedule.

We found this new colloid to be effective in tablet, granular and encapsulated powder form, but our patients expressed a decided preference for the tablets.

In cases of severe, chronic constipation, the harsh laxative used by the patients should be gradually reduced until finally omitted.

Sodium carboxymethylcellulose can be used as an adjunct in the treatment of hemorrhoids and proctitis.

We found this synthetic gum to possess most of the advantages and none of the disadvantages of other cathartics heretofore available to us.

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Achlorhydria and Its Clinical Significance in Diabetes Mellitus

By

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IN A RECENT MORTALITY INVESTIGATION, THE writer showed the extent to which it is now possible to control diabetes. Adjusted for age and sex, the ratio of actual to expected deaths in the group of diabetics who had adhered carefully to their treatment was practically normal. Equally gratifying was the finding that, as in the experimental animal, regardless of the severity of the diabetes, there is no evidence of an inherent tendency for the diabetes to become worse; that, in fact, provided treatment is followed carefully, there is an appreciable expectation of improvement of carbohydrate tolerance (1). This, however, does not warrant the conclusion that all of the problems in diabetes have been solved.

A random sample of a large group of diabetics will show that, though definite anaemia may not be common, a red blood cell count of 5,000,000 will be very uncommon. Of 281 consecutive cases, Joslin (2) reported 45 with cell counts below 4,000,000 — an incidence of 16 per cent. It is not stated whether they were hospital cases only or whether they reflected the experiences of the clinic for diabetes in general. For statistical purposes, it is the writer's practice to take 4,200,000 as the dividing line betwen anaemia, and no anaemia, corresponding as it does ordinarily to a haemoglobin value of, approximately, 85 per cent. With this standard, as Table 1 shows, the incidence of low red blood cell counts, was appreciably lower, but by no means negligible; of 500 consecutive examinations in his private office practice, 63 showed cell counts below 4,200,000 — an incidence of 12.6 per cent.

A random sample of a large group of diabetics, carefully questioned and carefully examined, will show that an appreciable percentage are suffering from diabetic neuritis. Estimates in the literature range between 0.6 and 57.3 per cent (3). Amongst 1,000 patients in Joslin's Clinic, Jordan (3) found 25 such cases — an incidence of 2.5 per cent. With the same classification of neuritic manifestations in diabetes, amongst 500 consecutive cases in the writer's experience, there were 31 —an incidence of 6.2 per cent (Table 1). Limited

Table 1

INCIDENCE OF ANAEMIA AND ACHLORHYDRIA ACCORDING TO AGE IN 500 DIABETICS SELECTED AT RANDOM

Age (Yrs.)	No.	ANAEMIA* No.	%	NEURITIS No.	%
-39	188	6	3.2	3	1.6
40-	312	57	17.7	28	8.9
All	500	63	12.6	31	6.2

*4,200,000 red blood cells or less.

significance is to be attached to smaller samples. Thus, amongst 100 cases only, to be referred to again, the incidence was 9 per cent. Joslin* has the impression that the incidence in his clinic now is larger than when Jordan published his paper in 1936.

A similarly selected sample will show that the incidence of digestive disturbances — coated tongue, loss of appetite, nausea, vague epigastric discomfort unrelated to meals, belching, bloating, fullness and fluid regurgitation after meals, abdominal distension, etc.— is high. To a certain extent this may be due to the high incidence of disease of the gall bladder and biliary passages in diabetes. In fact, the earliest reference to the pathology of diabetes was to the pathology of the liver; Mead first drew attention to the fatty infiltration in 1784 (4). Fatty infiltration of the liver is a common post-mortem finding in deaths due to diabetic

* Personal communication

coma; it is readily produced in the partially depancreatized animal, and, as Best and his associates have shown, the condition is greatly exaggerated in spite of insulin therapy when the choline content of the diet is kept low (5,6). Enlargement of the liver is common in uncontrolled diabetes (7) particularly in children. Priscilla White (8) found palpable livers in 40 per cent of her cases. In one case, the enlargement was such that the lower border was found in the pelvis (9). Two striking cases of fluctuation of the size of the liver with the degree of control of the diabetes were reported by the writer (10,11). In addition, there are the functional disturbances. In 1926, the writer (12) drew attention to the high incidence of excess quantities of bilirubin in the blood of diabetics and, in 1936, to a high incidence of excess excretions of uorbilinogen in the urine (13). More recently, Gray, Hook and Batty (14) reported a still higher incidence of liver disturbances in their group of diabetics; but that disease of the gall bladder and biliary passages is not alone the explanation of the high incidence of digestive disturbances amongst diabetics is suggested from a variety of pathological findings. Many years ago, Munro (15) drew attention to hypertrophy of the duodenal mucosa in diabetic coma. Still to be explained is the gastric haemorrhage in diabetic coma and also that with very severe insulin reactions. Nocturnal diarrhoea and nocturnal incontinence of faeces are other examples, and "diabetic indigestion" recently emphasized by Bassler and Peters (16) is another.

Another common occurrence amongst diabetics is achlorhydria. In 1931, the writer and his associates reported an incidence of 39 per cent (17) which then seemed very high. In the latest edition of their book, Joslin and his associates (2) record an average incidence of 32.8 per cent, based upon the experiences of eight different authors. More impressive, however, are Joslin's own experiences; whereas, gastric and duodenal ulcers are nearly always associated with hyperchlorhydria (18), amongst 58 cases with such ulcers, Joslin found no free hydrochloric acid in the first specimen in 21 — an incidence of 36.2 per cent(!) In 5 cases, there was no free hydrochloric acid even after histamine.

When two or more conditions are found in the same individual, it is sound practice to assume a common cause until proven otherwise. That the association of anaemia and achlorhydria, for example, may be causal rather than accidental, is suggested from the part that normal gastric juice plays in erythropoiesis; hydrochloric acid not only aids in liberation of iron from food materials, but also facilitates its conversion to the ferrous form which causes a discharge of reticulocytes from the bone marrow and an increase of red blood cells. Microcytic hypochromic anaemia, for example, which responds to ferrous iron is not an uncommon result of gastrectomy (18). Lack of free hydrochloric acid in the stomach was a frequent finding in the group of cases of anaemia reported by Joslin. In fact, it was the lack of free hydrochloric acid which led to the suspicion of a primary anaemia (2). Suggestive also is the influence of gastric acidity upon the absorption of iron. As pointed out previously (19) iron is absorbed mainly from the duodenum; and hydrochloric acid aids the absorption; whereas, a high pH in the duodenum facilitates formation of basic iron compounds which are very poorly absorbed. From a practical standpoint, therefore, assuming a causal relationship between the achlorhydria and anaemia in a case of diabetes, rather than merely prescribing iron, the more logical treatment of such a case would be to attempt to correct the pH in the stomach and duodenum by administration of hydrochloric acid.

Equally suggestive of a causal rather than an accidental association is the combination of achlorhydria and diabetic neuritis (19). It is important to note that, though thiamine is stable in gastric juice over a wide pH range — 1.5 to 8.0 — with a pH of over 8.0, it is readily destroyed. There is also evidence that achlorhydria may impair absorption of that part of the thiamine which has escaped destruction in the alkaline medium. Therefore, assuming a causal relationship between the achlorhydria and the neuritis, rather than merely adding thiamine to the diet of a diabetic with achlorhydria, the more logical treatment in such a case would be to attempt to lower the pH of the gastric and duodenal secretions by administration of hydrochloric acid so as to prevent destruction of the thiamine in the food materials. That hydrochloric acid may, alone, correct a vitamine B_1 deficiency in cases of achlorhydria is suggested from the observation that, in skin lesions associated with vitamine B_1 deficiency and deficiency of hydrochloric acid in the gastric juice, treatment with hydrochloric acid and B complex was found far superior to treatment with B complex alone (20).

In view of the above observations, 100 diabetics were selected at random from a group in whom gastric analysis had been performed, except with regard to age, in order to determine (a) the extent to which anaemia, neuritis, digestive disturbances and achlorhydria were associated with each other and (b) by subjecting the data to the proper statistical treatment, whether the associations were causal or accidental.

Because of the relationship noted in the previous study (17) between age and the occurrence of achlorhydria, the cases were divided into two groups, namely, (a) those of age 39 years and under and (b) those of age 40 years and over. In order that the percentage incidences of achlorhydria would be strictly comparable, at least with respect to the numbers of subjects from which they were calculated, the numbers of individuals in the two age groups were the same. Otherwise, as stated, the selection was random. The incidence of achlorhydria and the influence of age in this group are briefly summarized in Table 2.

Table 2

INCIDENCE OF ACHLORHYDRIA ACCORDING TO AGE

Age (Yrs)	No.	ACHLORHYDRIA No.	%
-39	50	9	18
40-	50	32	64
All Ages	100	41	41

INCIDENCE OF ACHLORHYDRIA

It will be noted that amongst these 100 diabetics there were 41 with achlorhydria, which fitted in very closely with the previously noted incidence of 39.0 per cent (17).

As would be expected from the known increase of the incidence of achlorhydria with age, the incidence in the older age group of these diabetics was about three and one-half times greater than amongst the younger subjects. More suggestive, however, of a causal relationship between diabetes and achlorhydria was the incidence in the younger age group, compared with that noted in normal individuals even of all ages. Amongst the 50 subjects under age 39 years, there were 9 with achlorhydria — an incidence of 18 per cent, which is about two to four times the incidence in normal individuals (21.22), and, approximately, that generally found in hospital cases, excluding gastric disease or pernicious anaemia. In a group of 100 normal individuals reported by Bennett and Ryle (3) there were four cases only of complete absence of free hydrochloric acid. Combining these data, therefore, with the previous findings (17); with the average based upon the experiences of eight different authors namely, 32.8 per cent (2); and with the above-mentioned Joslin's experiences with gastric and duodenal ulcers, it is clear that the incidence of achlorhydria is definitely higher amongst diabetics than amongst normal individuals.

ACHLORHYDRIA AND ANAEMIA

That there is a causal relationship between achlorhydria and anaemia is suggested from the data in Table 3, in which the above-mentioned 100 diabetics are divided into (a) those with and (b) those without achlorhydria and the incidence of anaemia determined in each group.

Table 3

RELATIONSHIP BETWEEN ACHLORHYDRIA AND ANAEMIA

Age (Yrs)	No.	NO ACHLORHYDRIA			ACHLORHYDRIA		
		No.	Anaemia* No.	%	No.	Anaemia* No.	%
-39	50	41	1	2.4	9	2	22.2
40-	50	18	2	11.1	32	9	28.1
All	100	59	3	5.1	41	11	26.8

*4,200,000 red blood cells or less.

It will be noted that, in the group as a whole, the incidence of anaemia was about five times greater in the group with achlorhydria than in those with no achlorhydria; whereas, of the 59 with no achlorhydria, 3 only had anaemia — an incidence of 5.1 per cent — of the 41 with achlorhydria, 11 — an incidence of 26.8 per cent — had anaemia. The findings are still more striking in the younger age group; whereas, of the 41 with no achlorhydria, 1 only had anaemia — an incidence of 2.4 per cent — of the 9 with achlorhydria, there were 2 with anaemia — an incidence of 22.2 per cent.

ACHLORHYDRIA AND NEURITIS

That there is a causal relationship between achlorhydria and neuritis is suggested from the data in Table 4, in which are recorded the incidences of neuritis amongst those with and those without achlorhydria.

It will be noted that, whereas, amongst those with achlorhydria, the incidence of neuritis was 17.0 per cent, in the group with no achlorhydria, it was 3.4 per cent only, and, here also, as in the data on anaemia, the findings were more striking in the younger age group; whereas, of the 41 with no achlorhydria, 1 only had neuritis — an incidence of 2.4 per cent — of the 9 with achlorhydria, also 1 only had neuritis, but the incidence was 11.1 per cent.

Table 4

RELATIONSHIP BETWEEN ACHLORHYDRIA AND NEURITIS

Age (Yrs)	No.	NO ACHLORHYDRIA			ACHLORHYDRIA		
		No.	Neuritis No.	%	No.	Neuritis No.	%
-39	50	41	1	2.4	9	1	11.1
40-	50	18	1	5.5	32	6	18.7
All	100	59	2	3.4	41	7	17.0

THE PROBABILITY OF CONCURRENT EVENTS

One of the theorems in statistics is that, if the separate probabilities of each of several independent events are respectively p_1, p_2, p_3 . . . p^n, the probability (P) of their all occurring together is the product of the independent probabilities — $P—p_1 \times p_2 \times p_3 \times \ldots p^n$.

The applications of this theorem to medicine are numerous. An example was its application in 1924 by the writer to the association of disease of the gall bladder and its passages with diabetes (24).

As a preliminary procedure, therefore, this formula was applied to the experiences with achlorhydria and anaemia and to those with achlorhydria and neuritis in the 100 cases shown in Tables 3 and 4 in order to determine whether these conditions were associated together more or less than would be expected if chance or random association were the only influencing factors which had brought them together. Thus:

ACHLORHYDRIA IND ANAEMIA

The probability of the occurrence of achlorhydria was taken as 40 in 100* or 0.40 = p_1.

The probability of the occurrence of anaemia was taken as 12.6 in 100** or 0.126 = p_2.

The probability of achlorhydria and anaemia occurring in the same person as the result of chance alone was, therefore, 0.40 x 0.126 ($p_1 \times p_2$) or 0.0504.

Actually, as Table 3 shows, the value was 0.268 (26.8 per cent).

Therefore, 5.3 times more of these diabetics with achlorhydria had anaemia than could be accounted for by chance association, thus pointing to a causal rather than to an accidental association.

* Average of incidences of achlorhydria noted in the present (Table 2) and previous (17) studies.

**Based upon the experiences with the above-mentioned 500 cases (Table 1).

ACHLORHYDRIA AND NEURITIS

The probability of occurrence of achlorhydria was again taken as 40 in 100* or 0.40 $= p_1$.

The probability of occurrence of neuritis was taken as 6.2 in 100** or 0.062 $= p_2$.

The probability of achlorhydria and neuritis occurring in the same person as a result of chance alone was, therefore, 0.4 x 0.062 ($p_1 \times p_2$) or 0.0248.

Actually, as Table 4 shows, the value was 0.17 (17 per cent). Therefore, 6.8 times more of these diabetics had neuritis than could be accounted for by chance association, thus, as in the case of anaemia, pointing to a causal rather than to an accidental association.

THERAPEUTIC TEST

ACHLORHYDRIA AND ANAEMIA

If, in fact, there is a causal relationship between achlorhydria and anaemia, hydrochloric acid should correct the anaemia to a certain extent at least, independent of any iron medication by liberating iron from the food materials; by aiding conversion of the liberated iron to the ferrous state, and also by aiding its absorption.

To test this possibility, 25 individuals were selected at random, except that (a) none had a red blood cell count higher than 4,200,000 and (b) in all cases, the diabetes was under good control, since improvement of the diabetes in a poorly controlled case would alone probably tend to improve the anaemia to a certain extent by the general improvement of nutrition. In each case, therefore, the only change of treatment was the addition of hydrochloric acid, in the form of glutamic acid hydrochloride (5 grains, three times a day, before meals) to avoid the possible solvent action of hydrochloric acid on dental enamel. Such amounts of hydrochloric acid, it should be noted, may not be sufficient to allow the appearance of appreciable free acid in the stomach, but, nevertheless, as Goodman and Gilman have pointed out (25), for some unexplained reason, they are often effective in relieving the symptoms of achlorhydria.

In order to compare the effects, if any, of hydrochloric acid with those of administration of iron, in each case, at the end of one month, the glutamic acid hydrochloride was replaced by a preparation of iron, which contained 6 3/4 grains of ferrous carbonate, which was also to be taken three times a day. To determine the extent to which, if any, hydrochloric acid would aid the absorption of the added iron, at the end of one month of treatment with iron alone, the glutamic acid hydrochloride was again prescribed in the above-mentioned dosage with no change in the treatment with the iron for a period of one month. The combined data are briefly summarized in Table 5.

* Average of incidences of achlorhydria noted in the present and previous (17) studies.

**Based upon the experiences with the above-mentioned 500 cases (Table 1).

Table 5

EFFECTS OF TREATMENT WITH GLUTAMIC ACID HYDROCHLORIDE ALONE, IRON ALONE AND COMBINATION OF BOTH ON RED BLOOD CELL COUNT

(25 cases)

	Before Treatment	TREATMENT G	Fe	G + Fe
M	4.06	4.56	4.60	4.85
S	0.147	0.355	0.219	0.226
PEm	0.020	0.048	0.029	0.030
D		0.50	0.04	0.25
PED		0.052	0.056	0.042
D/PE D		9.6	0.7	5.9

M Average red blood cell count (millions).
S Standard Deviation
PEm Probable Error of Mean
D Difference between Means
PED Probable Error of Difference

It will be noted that, following treatment with the glutamic acid hydrochloride alone, the average red blood cell count had increased from 4,060,000 to 4,560,000, and that the difference of 500,000 cells was significant may be seen from the ratio of the difference to its probable error. With a ratio of 9.6, it may be calculated that the chances against this average increase of red blood cells having been accidental were many millions to 1.

Following the treatment with the iron alone, it will be noted that practically no change had occurred in the average red blood cell count. From the ratio of the difference to its probable error, that is, 0.71, it can be shown that the average increase of 40,000 cells was not significant. That the increase of the red blood cell count following the treatment with glutamic acid hydrochloride had, however, been maintained suggests that, having fortified the diet with inorganic iron in a ferrous state was itself beneficial, in spite of the harmful effects of a high pH on absorption of iron, by at least having made it unnecessary to rely upon liberation of iron from its organic combination in the diet.

The last column clearly shows that the best result was obtained by the combination of glutamic acid hydrochloride and inorganic iron. It will be noted that, following this combined treatment for the same period of time — approximately one month — there was a further increase of the red blood cell count, and that the average difference noted — 250,000 cells — was significant may be seen from the ratio of the difference to its probable error. With this ratio of 5.9 it may be calculated that the chances against the occurrence of this increase having been accidental were over 10,000 to 1.

As a control, the above experiment was repeated in 25 other cases, except that the treatment with the inorganic iron preceded the administration of the glutamic acid hydrochloride. The combined data are briefly summarized in Table 6.

Table 6

EFFECTS OF TREATMENT WITH IRON ALONE, GLUTAMIC ACID HYDROCHLORIDE ALONE AND COMBINATION OF BOTH ON RED BLOOD CELL COUNT

(125 cases)

	Before Treatment	Treatment Fe	G	G + Fe
M	4.04	4.46	4.36	4.68
S	0.178	0.346	0.341	0.264
PEM	0.024	0.046	0.046	0.035
D		0.42	0.10	0.32
PED		0.052	0.065	0.058
D/PED		8.0	1.5	5.5

M Average red blood cell count (millions)
S Standard Deviation
PEm Probable Error of Means
D Difference between Means
PED Probable Error of Difference

It will be noted that the iron treatment was followed by an increase of the average number of red blood cells, and the diffference was significant. With a ratio of the difference to its probable error of 8.0, it may be calculated that the odds against this average difference of 420,000 red blood cells having been due to chance were almost 15,000,000 to 1. The iron treatment was then replaced by glutamic acid hydrochloride, which was continued for an approximately similar period of time. At the end of this period there appeared to be a slight reduction of the red blood cells — an average of 100,000, but that this difference was of very little significance is clearly seen from the ratio of the difference to its probable error, which was 1.5 only. With such a ratio, it may be calculated that the odds against the difference of 100,000 red blood cells having been due to chance were about 2 to 1 only. Much more significant was the difference, when this treatment was replaced by the combination of glutamic acid hydrochloride and iron. This, it will be noted, resulted in an average increase of 320,000 red blood cells, and the ratio of the difference to its probable error was 5.5. With such a ratio, the odds against the difference having been due to chance were over 2,000 to 1. Incidentally, the above findings are an example of the limited significance of average values in such studies, unless each is judged by its probable error.

Achlorhydria and Neuritis

In Table 4 are noted the high incidences of neuritis in the group of cases with achlorhydria, regardless of age. It is also shown that, according to the probability of concurrent events, 6.8 times more of these diabetics with achlorhydria had neuritis than could be accounted for by chance association. Interpretation of the results of treatment with hydrochloric acid, however, is more difficult than in the case of anaemia, since it is necessary to rely upon such clinical findings as subjective signs, etc. Interpretation is, however, simplified to some extent if the observations are restricted to severe cases, that is, those with pain in an arm or a leg, and not only more severe at night, but sufficiently severe to interfere with sleep without the aid of a sedative; marked paresthesias, rapid progression of the weakness, etc. Interpretation is further simplified by including only those in whom the diabetes was under good control, so as to exclude as much as possible beneficial effects from adjustment of the diabetes. Also, in cases in which vitamine B_1 had been prescribed, the selection should be restricted to those cases in which not only had no beneficial effects been noted from the vitamine, but also in which the vitamine had been discontinued for at least *one month before the hydrochloric acid* treatment had been instituted. If, with such selection, improvement of the neuritis is noted following use of hydrochloric acid, the chances are that the improvement noted following treatment with the latter was causal rather than accidental. The following are examples:

Hosp. No. 320/42. A male, 49 years, was admitted to The Montreal General Hospital (Medical Service of Dr. C. C. Richard) on Jan. 28, 1943, complaining of diabetes, which had been discovered six months previously, loss of weight, weakness and numbness of the feet.

The clinical findings were essentially negative, except for pallor, carious teeth, increased arterial reflexes in the fundi and a somewhat enlarged prostate. Except for the diabetes and the anaemia (red blood cell count — 3,240,000) all of the routine laboratory findings — urine, stools, blood urea nitrogen, van den Bergh, etc. — were negative. He had been told by a physician that he had syphilis. Of this, Dr. Richard found no clinical evidence, and the blood Wassermann and Kahn tests and the cerebro-spinal fluid tests for syphilis were negative.

The diabetes was under poor control on admission, but was rapidly brought under control by Dr. A. F. Fowler on a diet consisting of, approximately, 250 grams of carbohydrate, 45 grams of fat and 100 grams of protein and 20 units of protamine zinc insulin once a day: the urines were kept free from sugar and acetone bodies, and the blood sugar, in the fasting state, which was 0.262 per cent on admission, was reduced to 0.121 per cent only.

On Jan. 5, 1944, he complained of pain in the legs which, he stated, had been more severe during the night. Thereafter, the history was uneventful, and he was discharged from the hospital on Jan. 12, 1944.

On Feb. 18, 1944, he was readmitted (Hosp. No. 1111/44) with a history that, since his discharge, pain in both lower extremities had increased to such an extent that he could "stand it no longer." The clinical findings, other than the pain, were essentially the same. The diabetes, in fact, was found under such good control that the insulin was reduced from 30 to 20 units and kept at that level with a maximum blood sugar in the fasting state of 0.140 per cent. The X-ray findings in the lower extremities were slight bone atrophy of the phalanges of the heads of the metatarsal bones of both feet and marked calcification of the walls of the arteries. He was referred to the Sub-Department of the Peripheral Vascular Disease for investigation (skin temperature, oscillometric readings, etc.) for investigation of the possibility of vaso-spasm, but no evidence of the latter was found. On Feb. 24th — six days after admission — the pain had become very severe. The Interne's note read "Patient groaning, complaining bitterly of pain in the feet" For this, he was given salicylates, codeine and barbiturates, in the usual doses, with little relief. He left the hospital against advice on Mar. 6, 1944.

On May 3, 1944, when he consulted the writer, he stated that he not only had had no relief from pain since he left the hospital, but it had become so severe, particularly at night, that his physician had found it necessary to resort to morphine, the dose of which had to be increased so that he was then taking 3 grains a day.

From his appearance, it was obvious that he was ill and

in much pain, though the pupils were still contracted from the last dose of morphine; the skin was pale and moist and his conversation was repeatedly interrupted by moans. He weighed 112 1-2 pounds only in clothes (Height—63 inches). Since his naked weight when he left the hospital on Mar. 6, 1944 was 116 pounds, allowing about 8 pounds for clothes, he had lost, approximately, 12 pounds since then.

The diabetes was under good control; the urine was free from sugar and acetone bodies, and the blood sugar was practically normal, namely, 0.129 per cent. The red blood cell count was 3,100,000 and the haemoglobin 60 per cent.

Both feet were warm; pulsations were elicited in the dorsalis pedis, posterior tibial and popliteal arteries of both sides, and the patellar reflex was present on both sides, though the left was less active than the right. The abnormalities were marked paresthesias, abnormal sensations to pin prick, marked weakness and, in fact, slight foot-drop on one side (right). There was no suggestion in the history of any attacks of intermittent claudication.

The first considerations were relief of the pain and means of dispensing with the morphine. The impression was that he would cooperate, since he stated that the morphine caused much nausea and also, periodically, vomiting. In fact, he vomited during the examination.* He was, therefore, advised to discontinue the morphine and, instead of it, was given a salicylate mixture, the equivalent of, approximately, 50 grains of acetyl-salicylic acid per day. For nights, he was given a bromide mixture corresponding to 60 grains of equal parts of sodium, potassium and ammonium bromide and also one and one-half grains of phenobarbital. Both were to be repeated if necessary. For the anaemia, he was given the above-mentioned preparation of ferrous carbonate. In addition to all of the above, he was given dilute hydrochloric acid, ten minims, three times a day before meals. The notes show that it was the intention to prescribe vitamine B_1 also at the next visit, if there was no appreciable relief from the pain.

At his next visit on May 22, 1944 — 19 days later — he looked and stated he felt better. There was less pain during the day, and he stated that he had been sleeping better at night. The foot-drop had disappeared, but the paresthesias were still marked. The diabetes was under satisfactory control. The red blood cell count had increased to 3,800,000 and the haemoglobin to 73 per cent. A further loss of weight, however, had occurred; he now weighed 108 pounds, but he stated that the weight had been stationary during the previous week. He complained of noises in the ears." The only change of treatment, therefore, was a 75 per cent reduction of the salicylates.

One month later (June 22, 1944) a still further improvement was noted in his general condition. He stated that he had been sleeping well and had had pain occasionally only. The paresthesias were still present, but they were definitely less marked, all of which fitted in with the increase of weight to 115 pounds, and the increase of red blood cell count to 4,100,000 and the haemoglobin to 83 per cent. He was now advised to discontinue the salicylates and to reduce the bromide dosage 50 per cent, but to make no change of the barbiturate, iron and hydrochloric acid dosages.

On July 27, 1944, there was a still further improvement. The pain had disappeared; he had been sleeping well at night; the paresthesias were noted periodically only; the weight had increased to 124 pounds; the red blood cell count to 4,4400,000 and the haemoglobin to 85 per cnt. He was now advised to discontinue the bromides and the barbiturate, but to continue with the iron and hydrochloric acid.

On Nov. 3, 1944, a further improvement of his general condition was noted and, at the next visit on March 1, 1945, he looked and stated he felt, "very well"; and he stated that he had been working 12 to 13 hours a day and sleeping 7 to 8 hours a night for over a month; the weight had increased to 151 pounds. The red blood cell count was 4,600,000 and the haemoglobin 93 per cent. The iron treatment was therefore, discontinued, but he was advised to continue with the hydrochloric acid. Since then, the history has been uneventful, except that he has become careless with the diet.

*The tests for free hydrochloric acid in the vomitus were negative.

The experiences with two somewhat similarly severe cases (M. J. M. and H. St. M.) may be noted here, though the diagnosis of the type of neuritis was not as simple. In both cases, however, the experiences pointed similarly to benefical effects of the hydrochloric acid treatment.

Both were of advanced ages — 72 and 79 years respectively; both had sciatic nerve involvement and, also, fairly advanced arteriosclerosis, with absent pulsations in the dorsalis pedis and posterior tibial arteries; both had hypertension and, in both, the picture was complicated by osteoarthritic changes. In the case of M. J. M., alcohol was an additional complicating factor. In both, the hyperglycaemic type of neuritis appeared to be excluded, in view of the satisfactory control of diabetes; but, because of the advanced ages and the arterioscelerotic and osteoarthric changes. It was difficult to rule out the possibility of the circulatory and the degenerative types of neuritis. In neither case was there any history suggestive of attacks of intermittent claudication. That each was a case of typical diabetic neuritis, however, seemed clear from the fact that the neuritis was the major complaint; the onset of the pain had been sudden and much more severe at night; there had been rapid progression of weakness of the muscles and the paresthesias were marked.

That the diabetes was not an important contributing factor may be seen from the following ten consecutive blood sugar determinations in each case:

M.J.M.:	0.153	0.111	0.125	0.166	0.100
	0.100	0.143	0.143	0.111	0.120
H.St.M.:	0.133	0.099	0.085	0.114	0.090
	0.111	0.111	0.100	0.120	0.133

Following institution of the treatment with the hydrochloric acid, in the case of M.J.M., the neuritis had completely cleared up within less than a month; treatment was instituted on June 6, 1943, and, at his visit on July 5, he stated that he had been completely free from all symptoms for about a week previously.

In the case of H.St.M., the pain when he was first seen was so severe that he was unable to sit in a chair. He was, therefore, admitted to the hospital and, as records show (Hosp. No. 2723/44) the pain had so decreased following the treatment with hydrochloric acid that he was able to leave the hospital eleven days later. At his visit on Oct. 11, 1944, seven weeks later, he was completely free from all symptoms.

It would thus appear that, in both of these cases, the neuritis had been due to deficiency of vitamine B_1 which required no other treatment than lowering of the pH in the gastric and duodenal secretions, so as to prevent destruction of the vitamine B_1 content of the diet.

The idea that vitamine B_1 deficiency might explain typical diabetic neuritis is not new.* Needles (27) found no deficiency of this vitamine in the diets of his cases of neuritis, but the possibility of its destruction by high pH in the stomach and duodenum were not considered. The possibility of defective absorption is mentioned, but apparently no experiments had been made to test this possibility. A relative deficiency as a result

of a high carbohydrate intake and also possibly loss due to polyuria (28,29) may at times, be a consideration. In the above-described cases, however, there had been no change of the carbohydrate intake during the period of observation, and, as the diabetes was under good control, there was no polyuria.

That destruction of the vitamine B_1 in the diets of both of these cases was the dominant factor in the production of the neuritis is also suggested from the decalcification of the bones of the feet in both of these cases and from the known relationship between the pH in the duodenum and absorption of calcium. As pointed out previously (19) in addition to vitamine D and other substances in the diet for normal bone metabolism, efficient absorption of calcium from the diet is also essential. The evidence of the many attempts to correlate impaired absorption with the decrease in the solubility of phosphates of calcium in high pH media is confusing, but that soluble calcium salts are essential and that an acid reaction in the upper part of the intestinal tract aids in solution of calcium compounds seems clear from a number of observations. For example, rarefaction of bones of puppies following gastrectomy may be prevented to a large extent, and partially corrected, by addition of soluble calcium salts to the diet (18). Relevant here, therefore, is the fact that the acid phosphate of calcium is more soluble and, therefore, more readily absorbed, than the basic phosphate, and whether calcium is primarily in the acid or basic form depends upon the pH of the medium. A priori, therefore, any condition which tends to decrease the acidity in the duodenum (increase the pH) tends to impair absorption of calcium and achlorhydria is one of these conditions.

Use of hydrochloric acid for the neuritic manifestations of diabetes is not new, but evaluation of the results reported — failures and successes — is difficult because of failure to differentiate between the different types of neuritis met with in diabetes; failure to differentiate between cases with achlorhydria and those with normal gastric acidities, and also lack of control by use of two or more therapeutic measures at the same time. As the literature shows, differentiation of the types of neuritic manifestations as by Jordan (3) and Treusch (30) have been exceptions, and, as is well known, adjustment of the diabetes alone suffices in most cases to improve neuritis of the hyperglycaemic type. Here the dominant factor is probably a toxic one, rather than vitamine deficiency. With poor control of the diabetes fatty infiltration of the liver is common, and with fatty infiltration, the probability, as the writer has shown (11), is that there is also some impairment of the detoxifying function. Proper conclusions from simultaneous adjustment of the diabetes and administration of hydrochloric acid in such cases is thus obviously difficult. That achlorhydria is not the only factor, even in typical diabetic neuritis, is suggested from the resistance to treatment noted at times even in such cases, though, here, a factor in practically all of the writer's cases had been the long duration of the neuritis before the hydrochloric acid treatment had been instituted and thus possibly development of irreparable changes in the nervous tissues. Three cases only, however, regardless of how striking the findings may have been, do not afford proof of the effectiveness of any treatment upon any disease. The above three cases were cited merely because (a) they were amongst the earliest experiences with hydrochloric acid (b) the neuritis in each case was very severe and the findings, therefore, more significant and (c) in each case it was possible to differentiate fairly clearly between typical diabetic neuritis and the hyperglycaemic, circulatory and degenerative types. Since then, however, the writer has carefully controlled data of use of hydrochloric acid, with and without vitamine B_1 therapy, in a large group of cases, which will the subject-matter of a separate communication. In this study, the subjects are being grouped according to (a) the type of neuritis (b) the degree of control of the diabetes and (c) the treatment otherwise — vitamine B_1 alone for a long time; hydrochloric acid alone; hydrochloric acid preceded by vitamine B_1, and hydrochloric acid and vitamine B_1 combined.

ACHLORHYDRIA AND DIGESTIVE DISTURBANCES

On much more speculative grounds than the association of anaemia and neuritis with achlorhydria is the association noted between the latter and digestive disturbances. The data, however, are sufficiently suggestive and, as will be noted, of sufficient practical importance to warrant their publication so that others with similarly large groups of cases and laboratory facilities may add their experiences.

As stated, a random sample of a large group of diabetics will show that the incidence of digestive disturbances — coated tongue, loss of appetite, nausea, vague epigastric discomfort unrelated to meals, belching, bloating, a sense of fullness and fluid regurgitation after meals, abdominal distension, etc. — is high. Also, though the symptoms of achlorhydria are poorly defined the above, it should be noted, correspond almost exactly with the syndrome of achlorhydria described by Goodman and Gilman (25) and, for which, according to these authors, hydrochloric acid has been found effective in a significant percentage of cases.

A causal rather than an accidental association between achlorhydria and digestive disturbances is suggested from a number of experiences. For example, all ten cases of diarrhoea of diabetes reported by Bowen and Aaron (31) had achlorhydria, and, in Joslin's group, 14 of 29 cases showed achlorhydria even after histamine (2). Achlorhydria is frequently associated with the alternating constipation and diarrhoea of diabetes and also with the nocturnal incontinence of faeces. Thus, as Shay, Gershen-Cohen and Fels (32) have pointed out, it would appear that anacidity is of real clinical significance; that it not only indicates a loss of gastric function, but also conditions disturbed physiological states in parts of the body often quite remote from the stomach. Gradwohl (33) noted improvement

*For literature, see Ref. Nos. 2, 3 and 26.

of symptoms following use of hydrochloric acid in cases of diabetes with achlorhydria.

How achlorhydria might account for digestive symptoms is suggested from the known facts about the pH in the gastro-intestinal tract and how the latter may influence bacterial activity. Normally, even the secretions of the resting stomach contain appreciable amounts of free acid. In general, the free hydrochloric acid and total acidity of gastric juice are such that its pH ranges between 0.9 and 1.5, which accounts for its powerful antiseptic properties; streptococci, staphylococci and B.Coli are readily destroyed. As a rule, therefore, the duodenal contents are virtually sterile. In the duodenum, the acidity varies in proportion to the acidity of the chyme from the stomach, and the volume of alkaline fluids especially from the pancreatic juice. The type of food and stage of its digestion are also factors — meat tends to increase the acidity. As a rule, the pH ranges between 6 and 7 and is thus still on the acid side. In the small intestines, below the duodenum, the reaction is also still as a rule acid, though only slightly, due chiefly to the organic acids produced by the fermentative bacteria — acetic, butyric, lactic from carbohydrates, etc. The pH then increases so that faeces are usually either neutral or alkaline (ph 7.0 - 7.5), all of which influence the bacterial flora. In general, beginning with the duodenum, bacteria are found in increasing numbers, until they may account for 20 to 30 per cent of the dry weight of faeces and 50 per cent of its nitrogen. In the small intestines, their action is, as stated, dominantly fermentative; whereas, in the large intestines, the dominant action is putrefactive, and some of the products of this putrefaction are toxic — tryamine, ethylamine, indole, skatole, phenol cresol, histamine, etc. Normally, however, the large intestine is well equipped to resist passage of toxic products into the blood stream, and, as a further protection, there is the powerful detoxifying capacity of the liver to deal with toxic products that have passed the intestinal barrier and entered the portal circulation. For example, though normally there are about 50 mgms. of indole in 100 gms. of dry faeces and, though, as much as one gram of indole administered orally may not produce any symptoms and, even, 2 grams cause some dizziness and slight headache only (18), with failure of the detoxifying function of the liver, administration of as little as 25 mgms. may produce loss of appetite, belching, nausea and headache (11).

With achlorhydria, the picture changes. It is only so long as the micro-organisms of the acid producing type flourish that any bacteria from the large intestines which may have invaded the small intestines are unable to gain a foothold. Even with temporary achlorhydria, the duodenum may be rapidly invaded by micro-organisms from the colon (18) and the combination of alkalinity and lack of available oxygen favour the growth of obligate anaerobes in the metabolism of which reducing reactions predominate; bilirubin is reduced to colourless urobilinogen, sulphur and even sulphates to hydrogen sulphide. Many dyes and pigments (for example, methylene blue and litmus) are decolourized, bismuth salts are converted into the suboxide, but more relevant here is the increased production of the above-mentioned putrefactive substances (34). Furthermore, the small intestines are not as well equipped as the large intestines to resist passage of toxic products into the blood stream (18). In view of the above observations, an attempt was made to determine the extent to which, if any, the above-mentioned digestive disturbances are due to intestinal putrefaction as the result of achlorhydria.

Tests of Putrefaction

Of the numerous tests of putrefaction in the intestinal tract, those for indican in the urine were selected for this study for a number of reasons. Indican is derived from indole, which is one of the products of putrefaction which is toxic. Also, differing from the other ethereal sulphates is the fact that the latter are derived from protein metabolism, whereas indican arises, in great part, if not wholly, from putrefaction. That it may alone be taken as a rough index of the extent of the putrefaction changes is generally accepted (18,34, 35). Indican itself is not toxic. It is well-known that large amounts of indican may be found in the urine of apparently healthy individuals. It, therefore, would not account for the above-mentioned digestive disturbances. As in the case of the increase of the blood urea nitrogen in uraemia, however, an excess might point to excess production of other products which are toxic, and which are not being detoxified as readily as indole. Suggestive, for example, are the high incidences of indicanuria noted in gastro-intestinal conditions associated with headache, nausea, vomiting, etc. Suggestive also were Soper's (36) findings in his study of "toxic headache", in the diagnosis of which nasal sinus conditions, eye disorders, syphilis, allergy, hypertension, etc., were excluded; amongst a group of 696 such cases, excess quantities of indican were found in 85 per cent. As a preliminary step in this investigation, therefore, an attempt was made to determine the incidence of excess indicanuria amongst diabetics, compared with the general incidence.

Selection of Tests for Indican

Normally, the excretion of indican ranges between 4 and 20 mgms. per day. Quantitative tests such as Ellinger's (37), Askenstedt's (38), or Parker's modification of the latter (34) are, however, time-consuming and, therefore, not practical on a large scale. Provided, however, that the intensity of the colour produced by urine with indican concentration which correspond to the upper limit of the normal excretion is taken as the standard of normality, and that careful attention is paid to details — use of freshly voided urine only; removal of interfering substances; uniform proportions of urine and reagents*; allowance for maximum colour development, etc.,—and provided the conclusions are statistical —based upon a large number of observations and not upon simple tests—such simple qualitative procedures as the Obermeyer, Jolle and Jaffe yield useful information. They are not, however, equally sensitive. The Jaffe test is the least satisfactory due to the ease with

the extent to which this test is of value in the routine managment of the diabetic.**

SUMMARY

A study was made of the occurrence of anaemia, neuritis and digestive disturbances in diabetes mellitus and their association with achlorhydria.

The association of each of these conditions with achlorhydria was more than would be expected if chance or random association were the only influencing factors which had brought them together.

On the assumption that the anaemia in many cases of diabetes with achlorhydria is due to a high pH of the duodenal secretions which interferes with liberation of iron from the food materials; with its conversion to the ferrous form and also with its absorption, an attempt was made to treat the anaemia with hydrochloric acid only. Statistically, this resulted in an increase of the red blood cell count. That the difference — average increase of red blood cell count — noted was significant was found by the ratio of the difference to its probable error.

On the assumption that typical diabetic neuritis is due to a combination of destruction and defective absorption of Vitamine B_1 due to a high pH of the gastric and duodenal secretions, an attempt was made to treat such cases of neuritis with hydrochloric acid only. The results in the three cases of severe neuritis cited suggest that this is probably the correct explanation.

A study was made of the occurrence of excess excretions of indican in the urine in diabetes mellitus and, compared with that noted in non-diabetics, the incidence was high and definitely higher amongst a group with achlorhydria than amongst the control group. The association of the excess excretions with achlorhydria was more than would be expected if random or chance association were the only influencing factors which had brought them together.

The probable relationships between achlorhydria and other disturbances met with in diabetes mellitus are briefly discussed.

** Even if determined quantitatively, the urinary excretion of calcium is alone of limited value in determining the degree of its absorption, since it may account for anywhere from 10 to 40 percent of the total output. Therefore, still less indicative of the degree of absorption of calcium is the Sulkowitch test, since, even as modified by the writer, it is qualitative only. Like the percentage of sugar in the urine, however, averages based upon very large numbers of tests might yield useful information, provided they are subjected to the proper statistical treatment to determine their significance.

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The Palpatory Examination of the Paucreas: Description of a New Method

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The pancreas has long been of clinical interest because of its varied and important functions. Detection of pancreatic pathology even today is difficult because of the lack of simple diagnostic procedures, something which the practitioner has long awaited. The work of Obraztzow and Hausmann and that of Chauffard and Rivet on the *zona pancreatico-choledochica* and of Dejardins on the *point douloureux* for the head of the pancreas, represent clinical progress, and we refer also, in the Polish literature, to the Witold Orowski method (1910) which permits examination of the tender point of the head of the pancreas, independently of the variable position of the umbilicus.

I have previously described a palpatory method for pancreatic examination in 1935 and a "point douloureux" for the body of the pancreas determined by my palpatory method in the dorsal position. I have noted the trophic changes of the skin in the epigastrium as a new sign of chronic pancreatitis in 1937. In 1946 and 1947, I described my second palpatory method in the standing and sitting positions.

In 1943, Professor P. Mallet-Guy described an interesting method of manual examination of the pancreas in which he determines the tender point by deep palpation in the left hypochondrium. By comparing the results of my own methods, in the supine and standing positions, with the method of Mallet-Guy in April, 1946, I noticed that these results, with the patient lying on his right side, are much better if performed by the method which I elaborated in detail.



Fig 1 Grott's first palpatory method of pancreas in dorsal position (1935)

THE MODIFICATION OF GROTT

With the patient lying on his right side, the physician stands in front of him, using his right hand for the examination and employing his left hand on the lower part of the lateral aspect of the patient's thorax. In order to determine if a tender point can be found in the body or tail of the pancreas, whether the organ be enlarged or not, we palpate deeply with the right and in the upper part of the mesogastrium and in the left epigastrium, trying to push the movable viscera from left to right to facilitate palpation. The examining hand is pressed deeply till it reaches the left edge of the vertebral column and until the point is reached where the pancreas crosses it, and any tenderness or enlargement of the organ noted. In the second stage of this examination we attempt to palpate the tail of the pancreas by starting in the left hypochondrium, going deeply, and diverting the left rectus muscle to the right, and eventually noting if either tenderness or enlargement is present in the tail of the organ. The essential point here is getting outside the lateral edge of the left rectus muscle. An X-ray check-up by Prof. Misiewicz, after a barium meal, indicated that the stomach and duodenum during such an examination are pushed forward, thus permitting the examining hand to reach the space between the stomach and the vertebral column.



Fig. 2. Grott's second palpatory method of pancreas in standing position (1946-1947).

EXAMINATION WITH PATIENT LYING ON LEFT SIDE

The palpatory method above-described lends itself equally well to an examination of the head of the pancreas, merely by placing the patient on his left side. The right mesogastrium is then explored in a similar manner and any enlargement or tenderness in the head of the pancreas ascertained.



Fig. 3. Prof. P. Mallet-Guy's palpatory method of pancreas (1943).

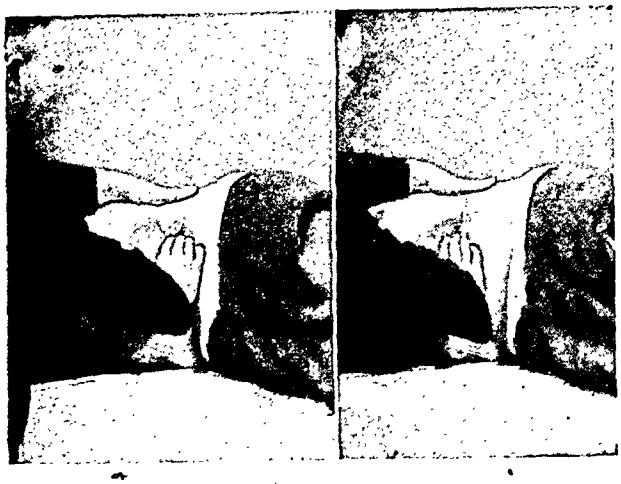


Fig. 4. Grott's third papatory method of pancreas in lying position on right side (1947).

I have now employed these methods for nearly two years and the results suggest that this easy method is one of great clinical usefulness, because not only is pancreatic enlargement detected, but a tender spot is located in the head, the body or the tail of the organ. So much for a bare description of the method. In my next paper I will reveal details of its usefulness, as compared with other methods.

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NUTRITION

Studies On Serum Carotene In Man

By

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Our present knowledge of carotene metabolism is based mainly on animal experimentation. Carotenes are considered to be pro-vitamins A and their conversion is said to occur in the liver. Absorption and utilization of carotene have been extensively studied under varied experimental conditions whereby the amounts of dietary fats, the oils used as solvents as well as other factors were considered (21, 17, 15). Seasonal variations of the carotene content of butter fat and their effect upon the vitamin A and carotene levels of the serum have been reported (14), and the relative provitamin A activity of carotene after oral and parenteral administration in rats has been investigated (19); adequate amounts of α—Tocopherol are essential for the conversion (13).

Knowledge of carotene metabolism in man is scanty whereas considerable information is available on vitamin A metabolism in man under normal conditions and in disease. Alteration of carotene metabolism occurs in some instances of liver disease and in sprue. In ac-

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tive stages of cirrhosis of the liver, lower levels of carotene were found than in severe acute hepatitis (6); the difference was presumably due to the prolonged duration of the former disease. Strikingly low carotene levels in serum were found in active sprue (4) and even during remission, the tendency to low carotene levels often persists although the morphologic blood status and bowel function have greatly improved (3). Profound disturbance in the metabolism of all fat-soluble vitamins in sprue is the underlying cause of these changes (3,10).

Considerable information regarding abnormalities of vitamin A metabolism was obtained by the application of the oral vitamin A Tolerance Test under standard conditions (1, 4, 5, 6). It seemed therefore profitable to study carotene absorption in man under similar standardized conditions. The final aim was elaboration of a convenient Carotene Tolerance Test for the study of physiological and pathological problems of carotene metabolism in man.

METHOD

For the estimation of carotene as well as of vitamin A in serum the Dann-Evelyn method was used on 6 - 10 ml. of fresh serum (macro-method) as well as the spectrophotometric micro-method of Bessly, Lowry et al. (9). In each individual the "fasting" serum level of carotene and vitamin A was determined; then the test dose of crystalline carotene (90% β—carotene, 10% α—carotene; General Biochemicals, Inc.) in a fat vehicle was administered.

It soon became evident that crystalline carotene decomposes up to 50% in a few weeks unless certain precautions (vacuum, darkness, and low temperature) are strictly applied. Therefore each ampule was opened only a few seconds before the required amount was removed for analytical purposes or for the use in tests. The ampule was immediately resealed in vacuo and kept in the dark. Frequently analytical control is advisable although with these precautions only an occasional moderate loss of carotene, up to 8%, was observed.

The test meal consisted of 60 to 180 mg. of carotene in butter or oil with one slice of white toast and one cup of tea. No other food was given for four hours and the individuals remained in bed. For the duration of the test (3-7 days), foods high in carotene or vitamin A (carrots, butter, etc.) were omitted from the diet. Even so, great variations in "fasting" carotene levels were observed between individuals and between some of our groups, which had been examined at different seasons (see Table I). These variations reflect the annual cyclic changes of serum carotene content of the average diet (14; Sobotka, Brickner and Kann (unpublished). However, they do not affect the significance of the trends observed during the three to seven days of the test.

ABSORPTION OF VARYING AMOUNTS OF CAROTENE IN BUTTER BY NORMAL CONTROLS

The first tests were performed with 60 mg. carotene administered in 12 gm. of butter to 3 normal individuals and 2 convalescing patients who had been afebrile for two weeks (Series A, Table 1). No significant rise in the carotene or vitamin A level was seen in this group except for one case (not included in the table) whose fasting carotene level was unusually high and who showed a great transient increase after 24 hours. There was nothing abnormal or unusual in this individual's clinical or laboratory findings; he admittedly consumed large amounts of yellow and leafy vegetables.

Upon doubling the amount of the test dose and vehicle (120 mg. carotene in 24 gm. of butter) a substantial rise in the carotene level was regularly seen (Series B). No effect was shown after four hours, but the highest values, up to twice the fasting level, were observed after 24 to 48 hours in nine cases without exception. This was followed by moderate increases of the vitamin A level 72 to 168 hours after ingestion of the carotene test dose.

A further increase of the test dose to 180 mg. carotene in 36 gm. butter in two subjects did not affect this picture (Series C). This offered no advantage, but impaired the palatability of the test meal. Thus, 120 mg. of crystalline carotene in 24 gm. can be considered a suitable dose for the attainment of an optimal, although slow, elevation of the carotene concentration of the serum.

THE EFFECT OF COTTONSEED OIL ON ABSORPTION OF CAROTENE

The question arose whether the composition of the fat used as a vehicle for carotene has any effect upon its absorption in man, since it is known that not only the amount of fat in the diet, but also the type of fat used, affects carotene absorption in animals. The rise in carotene level in three normal individuals who received 120 mg. carotene dissolved in 15 ml. cottonseed oil, was hardly perceptible and certainly inferior to the rise obtained when butter had been the vehicle for the same dose. (Series D). For man, therefore, butter represents a better vehicle for carotene than cottonseed oil.

EFFECT OF LECITHIN ON ABSORPTION OF CAROTENE FROM COTTONSEED OIL

In previous studies the effect of lecithin on absorption of fat and vitamin A was demonstrated (1, 4). Soybean lecithin had been used widely in shortenings and mayonnaise for its emulsifying effect. We assumed that the ability of lecithin to promote intestinal absorption of fat and vitamin A was also based on its emulsifying properties. Our original observations in man were extended by Slanetz and Scharf (22, 23) and Esch et al. (12) to the utilization of vitamin A by the rat and cow. The effect on fat absorption was later confirmed by Augur, Rollman and Deuel (8). The latter authors also confirmed that the addition of lecithin to fat lessened the susceptibility to diarrhea in rats and increased the digestibility coefficients of hydrogenated cottonseed oil. These observations are in good agreement with the original findings that addition of lecithin to the diet

TABLE I

CAROTENE ABSORPTION TEST

Series	Number of cases	Test Dose of Carotene mg.	Vehicle	Mu/g. Carotene in 100 ml. Serum (average ± S.D. of mean) c) Fasting	After 24	48	72	168 hours
A	4	60	12 gm. butter	82±10	89±12	96±11	80±11	80±13
B	9	120	24 gm. butter	122±17	166±17	172±13	147±17	122±15
C	2	180	36 gm. butter	164	196	209	203	
D	3	120	15 ml. CSO a)	162±24				
					168±19 d)	188±22		
E-F b)	8	120	15 ml. CSO x 9 gm. Soybean Lecithin	164±24				
					183±28 e)	178±19	166±10	
G	5	120	15 ml. CSO x 20 gm. defattened Lecithin	145±24	180±25	173±29	200±33	
H	3	120	15 ml. CSO; then 0.6 gm. dried ox bile	177±51	190±63	185±69	173±64	
I	3	120	15 ml. CSO; then 0.6 gm. Desoxycholic Acid	188±42	198±26	197±27		
K	2	-	0.6 gm. dried bile or 0.6 gm Desoxycholic Acid	223	218	213		

a) CSO - Cottonseed Oil b) 2 cases (F) received 12 g. Soybean Lecithin. c) The differences in the fasting level of serum carotene reflect its well-established seasonal variations. Group A was studied in December when the carotenoid content of the serum has reached its lowest level. The subsequent groups were investigated during the ensuing months until July (group K). d) After 4 hours: 168 mu/g e) After 4 hours: 180 mu/g.

exerted a favorable influence on food absorption (particularly fat, possibly vitamins) and on intestinal motility (7). It seemed, therefore, of interest to include lecithin in the study of carotene absorption in man.*

Nine or 12 gm. crude commercial soybean lecithin (Series E and F) were added to test meals consisting of 120 mg. carotene dissolved in 15 ml. of cottonseed oil. While this addition produced acceleration (see footnotes c and d of Table I) and intensification of carotene absorption, the results were more impressive when 20 gm. (Series G) defatted lecithin were used. The content of lecithin in this preparation was naturally higher since ca. 30% soybean oil, present in the crude commercial soybean lecithin, is omitted.

The serum carotene elevation obtained in Series E, F and G, may be compared with Series D. The maximal elevations of the serum carotene concentration after 24 hours or 48 hours, when defatted lecithin was employed, ran in the individual cases from 27 to 123 mu/g per 100 ml. and were, thus, much higher than any figures observed previously with cottonseed oil. Thus lecithin considerably enhanced the absorption of carotene in man; in fact, its addition improved carotene absorption from cottonseed oil to a level higher than that observed when butter was used as a vehicle.

According to Schall (18) the lecithin content of 100 gm. butter is 160 mg., that of lard, beef tallow and mutton tallow considerably lower (12 to 35 mg.), and that of cod liver oil only 4.8 mg. Other investigators found even higher concentrations of lecithin in butter, up to 1.5 to 2% (16). The higher lecithin content of butter is responsible for some of its characteristic qualities, like browning and foaming. The reported observations suggest that the superiority of butter to cottonseed oil as a vehicle for carotene is due to its relatively higher lecithin content, thus adding another reason for the customary supplementation of margarine with lecithin.

*The particular solubilizing effect of lecithin upon carotene in water has been described by Straus. (24).

EFFECT OF BILE ACIDS ON ABSORPTION OF CAROTENE FROM COTTONSEED OIL

In order to study the effect of bile and bile acids, capsules containing either 0.6 gm. dehydrated ox bile (Series H) or 0.6 gm. desoxycholic acid (Series I) were given to groups of three patients each immediately after ingestion of the test meal of 120 mg. carotene in 15 ml. cottonseed oil, accompanied by one slice of toast and one cup of tea. The bile acids exerted only a slight effect in accelerating the inherently poor absorption of carotene from cottonseed oil. Whereas there was usually no elevation of the serum carotene level four hours after the administration of the test meal, an average elevation of 11 mu/g per 100 ml. was found after four hours with the addition of dehydrated ox bile, and of 17 mu/g per 100 ml. with Desoxycholic acid. Although these rises are small, one gains the impression that the bile acids moderately accelerated the absorption of carotene from cottonseed oil. The addition of bile acids, however, failed to improve the intestinal absorption of carotene from cottonseed oil to the levels which were observed when butter was used as a vehicle (Series A, B).

In order to study the effect of the bile acids *per se* on the carotene concentration of the serum, two normal individuals were given 0.6 dehydrated ox bile or 0.6 gm. desoxycholic acid, respectively (Series K). After 4 and 24 hours no elevation of serum carotene was noticeable; on the contrary, the carotene levels showed a slight decrease (223 - 218 - 213 mu/g per 100 ml.).

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Nutrition Notes

The National Food Situation

Domestic food consumption per capita will probably not change much in 1949 from the 1948 average which was 12 per cent above prewar. Supplies of a few foods are expected to decline, but others will increase. Consumption of food per person in 1948 was at a somewhat lower rate than in 1947, whereas food prices averaged about 10 per cent higher. Retail food prices probably will remain high in 1949. The export demand for American foods will probably not show much decline, but less emphasis will be put on grains. Military procurement of food for troops and for *civilian feeding programs* may continue at about 1948 rates. In comparison with the prewar years 1935-1939, rates of food consumption will continue at a high level. Only per capita consumption of butter, dried fruit, potatoes and dry beans are likely to be lower. Consumption of most other livestock products and fruits and vegetables will be noticeably higher than in the prewar period (Courtesy, U. S. Bureau of Agricultural Economics).

Fluorine and Dental Caries

The decay of teeth is probably one of the oldest of human ills and the archaeolgists describe these defects in the teeth of the Stone Age man. The Ebers Papyrus, which is almost six thousand years old, describes dental diseases current at that time. Modern dentistry regards the provoking cause of dental caries as acids which are formed by the action of bacteria on sugar and other carbohydrate food particles in the mouth. The rather recent discovery of the value of fluorine in preventing this disease is one of the landmarks in the history of dentology. The discovery came about unexpectedly as a result of an investigation of an entirely different dental defect, viz., mottled enamel. Dr. Frederick S. McKay of Colorado and his associates in the U. S. Public Health Service traced the cause of dental fluorosis, as mottled enamel now is known, to water supplies, and by 1931, fluorine was incriminated as the cause of this disease. Seven years later it was noticed that people living in communities where the water contained fluorine, and who showed dental fluorosis, were strikingly free of cavities as compared with people who used fluorine-free water. This point was further proved to be true, and it was shown that about one part in a million of fluorine in the drinking water was an optimum concentration, because by using such water from birth, individuals were largely protected against cavitation on the one hand and fluorosis on the other hand. As pointed out by McLaren*, current social experiments are being carried out, and in Brantford, Ontario, for example, the effect of artificially fluorinated public water supplies is being studied over a ten-year period, during which time the dental history of a whole genera-

creased to the organisms, especially B. coli associated with the endocervicitis by the improvement in the general condition of the patients and the estrogens have enhanced value due to the eradication of the local infection. The essential factor in these observations appears to be the elimination of sucrose, whose presence in the diet promotes an imbalance in the intestinal flora, and apparently unfavorably affects general metabolism, at least in these cases of infecundity.

PILLOW, R. P. AND PALMER, L. J.: *Juvenile diabetics.* (Northwest Med., Feb., 1949, Vol. 48, No. 2, 101-104).

A study of 25 cases of juvenile diabetes of 20 years or more duration, shows a high incidence of premature vascular disease, usually first evident in the retina and next in the kidney. The heart, brain and general vascular tree also present degenerative manifestations. Whether this high incidence of vascular disease (atheromatous degeneration) indicates a direct result of altered carbohydrate metabolism or a concurrently altered fat metabolism is still an open question. If one is to believe that premature vascular disease occurs as a direct result of a poorly controlled diabetes, it is difficult to explain the exceptions which occur. Thus, some patients who have been poorly controlled diabetics over a long period of time, in spite of higher insulin dosage, may fail to reveal vascular disease after 15 years, while other patients with milder diabetes of much shorter duration show extensive damage. These exceptions to the rule suggest that in the majority, but not in all diabetics, there is a metabolic disorder which is not always an integral part of the primary disease. Nevertheless, close chemical surveillance of blood and urine should be done in all cases in order to approximate normal blood sugars as closely as possible.

BROWN, C. H.: *Idiopathic steatorrhea.* (Cleveland Clinic Quarterly, Jan., 1949, Vol. 16, No. 1, 52-58).

Monilia organisms are no longer considered the etiological factor in sprue. The essential cause of the disease is an alteration in the mucosa of the small intestine which results in an impaired absorption of fat, with consequent fatty diarrhea, macrocytic anemia due to lack of absorption of the intrinsic factor, osteoporosis and tetany from lack of calcium absorption, lack of vitamin D absorption, skin changes and lens opacities due to poor absorption of vitamin A, a hemorrhagic picture at times due to lack of vitamin K absorption, and glossitis and stomatitis caused by faulty absorption of viamin B components. Most paients encountered are not suffering from active sprue but its complications. In treatment the fat content of the diet should be kept low and increased as tolerated. Parenteral liver extract, 2 c.c. daily either crude or refined, is the sheet anchor of treatment. Folic acid at least takes care of the anemia but should not be used as an exclusive therapeutic measure. Vitamin B-complex, A and D and sometimes K are needed and calcium lactate used daily. In spite of the excellent results of treatment, the flat vitamin A tolerance curve persists, indicating that the basic difficulty is not corrected.

FENICHEL, N. M.: *Chronic headache due to masked hypothyroidism.* Ann. Int. Med., Sept. 1948, Vol. 29, No. 3, 456-460).

Twenty cases are presented in whom headache was associated with hypothyroidism and improved promptly on thyroid treatment. Practically none of these patients showed the signs of stigmata usually associated with myxedema. Suggestive features of such "masked" hypothyroidism are asthenia, sensitivity to cold, slow resisting pulse rate, and moderate hypotension. The B.M.R. should be determined in any patient complaining of persistant headache in whom no cause for the headache can be found. The author makes no attempt to explain the possible mechanism of headache in hypothyroidism. Only one of the cases was myxedematous.

JONES, E., TILLMAN, C. C., AND DARBY, W. J.: *Observations on relapses in pernicious anemia.* (Ann. Int. Medicine, Feb, 1949, Vol. 30, No. 2, 374-380).

Following the withdrawal of liver-extract, six out of twelve patients failed to show a hematological relapse over a period of 26 to 29 months. Eight to 12 months were required for relapse to appear in the six patients who did exhibit hematological relapse. The authors have attacked the problem of how to recognize such relapse in its early stages. It is always difficult to say what a given patient's pre-disease level of hemoglobin and red cell count actually were, and it is not entirely satisfactory to take, let us say, 4,000,000 red blood cells per c.c. as an absolute standard or to regard two successive blood counts falling below this level as an indication of relapse. It seems to them better to relate relapse to the red cell levels of the individual patient. By calculating the mean and standard deviation of counts on each individual patient for the preceding year of liver therapy, then two successive counts more than two standard deviations below his treatment mean could be regarded as the beginning of a hematological relapse. They also emphasize that the output of urobilinogen in the stools increases early in relapse and they feel that this indicates the importance of hemolysis in the pathogenesis of this disease.

MALMROS, H. AND HERNER, B.: *Treatment of pernicious anaemia with special reference to hypersensitivity to liver extract.* (Nordisk Med., Nov. 19, 1948, Vol. 40, No. 47, 2138 2140).

The author treated 17 cases of pernicious anemia orally with folic acid plus a stomach-liver preparation, two of whom developed neurological symptoms, so that injection treatment with liver extract, which had been discontinued because of pronounced allergic reactions, had to be resumed. The patients were first desensitized by the use of high dilutions of liver extract, and then more concentrated solutions, till treatment could be continued with ordinary doses of liver extract. To prevent allergic reactions 1/2 to 1.0 c.c. of 1/000 adrenalin solution was given a few minutes before each liver extract injection. The author stresses the point that if folic acid is combined with stomach-liver preparations in

Editorials

BRAVE NEW WORLD, IN THE THERAPY OF PERFORATED ULCER

Colonel Sam F. Seeley,* M. C. and his associates at the Brooke General Hospital, Fort Sam Houston, Texas, deserve some kind of recognition for doing something that, so far as we know, has not been done before. They have treated 34 cases of perforated duodenal ulcer, without operation, and without a single death. Their report is to be found in the February, 1949, issue of the Bulletin of the U. S. Army Medical Department. Decompression of the stomach by a Levine tube, intravenous fluids and a great deal of penicillin and sodium sulfadiazine, along with initial use of morphine constituted the chief therapeutic elements. They regard effective gastric decompression as the most important element, and this requires constant attention. Apparently these authors believe that such non-operative treatment, *if properly carried out,* has several advantages over surgery, the chief being a great reduction in mortality, but they emphasize that much caution is required for success. The article ought to be read by all internists, gastro-enterologists and surgeons. After reading it, one gains the impression that this is a piece of work that may exert an important influence on the treatment of ruptured peptic ulcer. It will require some courage to embrace such a method, but, provided the method is thoroughly understood, and that the *closest* observation of the patient can be assured, there seems no objection to using it.

We have become so accustomed to operate immediately a diagnosis of perforated peptic ulcer is made, that it will no doubt require time for us to become accustomed to thinking of this complication without at once thinking of surgery. Facts, however, are facts, and the article referred to covers every angle of the subject, and the conclusions of the authors appear to be indeed justified by the results which they have obtained. If their mortality figures continue to remain at a low level, to say nothing of the zero level, in their first 34 cases, it may be possible to attribute to Colonel Seeley and his associates success in beginning a revolution in the treatment of peptic perforation, and of presenting a distinctly life saving method.

WHO UNDERSTANDS THE ACUTE ABDOMEN

If any one subject has been "written to death" in the course of the past 30 years, it is the "acute abdomen",—an American term which has been accorded almost world-wide acceptance. The said writings have been so numerous, constant and repetitious that many practitioners skip the article once the have noted the title. Yet when presented with the acute abdomen in practic, is there anyone among us who ever feels perfectly at home or completely at ease?

We should remember, as Estrada and Nery (1) have recently emphasized that there is an acute medical abdomen and an acute surgical abdomen, and to be able to make the distinction unerringly is perhaps the most important job of all, and involves life or death for the patient. In most of the following conditions operation is usually contraindicated—coronary occulsion, pneumonia, pleurisy, meningitis, toxic goiter, influenza, malaira, tabes, lead poisoning, dysentery, dysmenorrhea, genito-urinary lesions, and biliary dyskinesia.

Careful history taking is of prime importance. Scout films, urinalysis and fecal examination and leukocyte counts may help. Rigidity of the right diaphragm, seen fluoroscopically, may indicate subphrenic abscess or liver abscess. Some of the clinical points to check upon are the presence of Argyll-Robertson pupils, blue lines at the gum margins, and cervical rigidity. The hernial orifices ought to be examined and a rectal examination never omitted. "Leukoytosis does not always mean an acute surgical abdomen nor does a normal count or leukopenia rule out immediate surgery".

When diagnosis is impossible, exploratory laparotomy ought to be done. Sometimes the diagnosis of acute medical abdomen is justified but it requires both skill and courage. If there is one irredeemable sinner in the abdomen, it is the appendix. We have all seen peritonitis from a perforated appendix without fever, without leukocytosis and with strangely little rigidity. We have also seen the Hippocratic facies, thready pulse and cold sweat leading irrevocably to death in the patient confidently diagnosed as "intestinal flu".

There is no greater test of a physician's scholarship, alertness and sound judgement than acute abdominal disease.

(1) Estrada, J. R. and Nery, P. T.: Diagnosis of acute abdomen. Acta Medica Philippina, April-June, 1948, Vol. IV, No. 4, 1-4.

NOTICE

A forthcoming issue of this Journal will contain an article entitled: **A PRACTICAL AND INEXPENSIVE SCREEN-TEST FOR CANCER**, by N. Philip Norman, M.D. and Anna M. Slicher, B.A. In this screentest, the diagnosis depends upon the character of the clot reaction pattern. The usefulness of this test is not limited exclusively to malignancy; other profound systemic disturbances frequently display disturbed clot retraction patterns. These are similar, but not identical, with that of cancer. The article will contain 28 photomicrographs illustrating the interpretation of the different clot retraction patterns which may be encountered.

This simple test requires a clean glass slide, a proper finger puncture and satisfactory magnification apparatus.

The authors emphasize that the test is not infallible. In their hands, however, it has proven to be 97% correct. Inexperienced investigators, who will use the test occasionally, can anticipate a greater percentage of incorrect diagnosis because of their unfamiliarity with the various clot retraction patterns.

This investigation may be considered an extension study of the original work of Doctor H. Leonard Bolen. This preview is published to establish priority rights for the authors.

*"Nonoperative Treatment of Perforated Duodenal Ulcer" b Col. Sam F. Seele, M.C., Edmund Hogan, M.D., Major Joseph R. Henry, M.C. and Major Harold F. Bertram, M.C., Bull. U.S. Army Med. Dept., Feb., 1949, Vol. 9, No. 2, 124-130.

Book Reviews

THE BRITISH ENCYCLOPEDIA OF MEDICAL PRACTICE: *Medical Progress 1949.* Butterworth and Co. Ltd., London, England.

This annual, edited by Lord Horder, has the indisputable advantages of pointedness and brevity. The material presented aims at describing only what the contributors consider to represent progress during the year just passed. In the present volume chief attention is directed to the following subjects,—streptomycin treatment of T.B., penicillin, folic acid, hypertension, cardiovascular surgery, vagotomy, the third stage of labor, phonocardiography, a poliomyelitis epidemic in 1947, metabolism of amino acids, changes in the British Pharmacopoeia. Many other subjects of course are dealt with. The general abstracts which form slightly more than half the volume are very exhaustive ones and unusually well-written and deal with all phases of practice. Anyone desiring to obtain an extensive impression of recent progress in medicine would probably gain it with least labor by reading this book. The book might be ordered from the Canadian Branch of Butterworth's, at 1367 Danforth Avenue, Toronto, Ontario. The cost of the volume is not stated.

NATURAL PRODUCTS RELATED TO PHENANTHRENE. By Louis F. Fieser and Mary Fieser, 704 pages. Reinhold Publishing Corp., New York, N. Y., 1949, $10.00.

Since publication of the second edition of this monograph in 1937, interest in the unique group of naturally occurring phenathrene derivatives has mounted to a high pitch and the literature has been expanded by the appearance of hundreds of papers on the chemistry, metabolism, pharmacology, and clinical applications of the important physiologically-active members of the series. It is a fully critical survey, and includes a number of new correlations and interpretations of data.

This monograph is addressed not only to chemists, biochemists, and medical investigators directly interested in the specialized field, but also to workers in other fields, who now have easy access to a wealth of new techniques of experimentation, new schemes of synthesis, and new theoretical concepts that have resulted from the spectacular advances in the chemistry of the steroids and related products.

General Abstracts Of Current Literature

EXPERIMENTAL MEDICINE

STOMACH

JANKELSON, I. R. AND MILNER, L. R.: *Digestive tract hemorrhage of undetermined origin: clinical and pathological observations.* (Rev. Gastroenterology, Sept. 1948, Vol. 15, No. 9, 692-695).

Ten rapidly fatal cases of massive digestive tract hemorrhage of undetermined origin are reported. The primary cause of these deaths was bleeding from the digestive tract. Post-mortem examination failed to reveal a definite source of bleeding. There were 9 males and 1 female in this series. The average age was 58.5 years. Five patients had hematemesis accompanied by melena while five patients had melena only. The fatal cases of digestive tract hemorrhages are more likely to remain unexplained, and in a considerable percentage of those who recover examination and/or operation fail to reveal the source of bleeding.

MISCELLANEOUS

DAY, E. M. A.: *The urinary excretion of 17-ketosteroids and of corticosteroid-like hormones by the new-born infant.* (Med. J. Australia, July 31, 1948, 122-124).

In 12 normal male new born infants the 17-ketosteroid excretion in the urine was determined and the levels did not suggest an excessive androgenic function of the adrenal cortex. (Four babies delivered by Caesarean section excreted comparatively large amounts of androgens). The amount of corticosteroid-like hormone excreted in the urine of seven normal male new born infants has been found to approximate in value per gram of adrenal tissue to figures given for normal adults.

DANCIS, J., BIRMINGHAM, J. R. AND LESLIE, S. E.: *Congenital diabetes insipidus resistant to treament with pitressin.* (Am. J. Dis. Child. March, 1948, Vol. 75, No. 3).

Recurrent bouts of fever in an infant were found to be caused by dehydration resulting from extreme polyuria The polyuria was probably not due to pituitary insufficiency since it did not respond to pitressin and since the patient's urine contained large amounts of an anti-duretic substance presumably derived from the pituitary. The excessive diuresis was probably due to a congenital anomaly of kidney function caused by the kidney's inability to respond to normal hormonal control.

SEAL, S. C.: *On the control and prevention of endemic cholera in the rural areas of Bengal.* (J. Indian Med. Assn., July, 1948, Vol. 17, 10, No. 319-321).

As a result of a survey of cholera endemic in rural Bengal, India, the author recommends three new features in the methods of control and prevention, (1) The method of anti-cholera revaccination by intracutaneous inoculation of one-tenth c.c. of the usual dose, (2) A segregation cottage for every village, built and operated on a voluntary basis, (3) A special endemic control unit consisting of a field and a laboratory section for each sub-division of Bengal. Improvement in communications in the rural areas is badly needed to facilitate these measures.

Trauma of the Pancreas - Experimental Study

By

H. L. POPPER, M. D.

CHICAGO, ILL.

EXPERIMENTAL STUDY

In an earlier paper the consequences of experimental injuries to the pancreatic duct were reported(1). In the dog, transection or lengthwise incision of the main pancreatic duct without ligature of the open ducts was not followed by any acute intraperitoneal process. When the dogs were starved before and after operation, the opening of the pancreatic duct was sealed by omentum. However, in dogs that had been fed pre- or postoperatively, or that had received cholinergic drugs, intraabdominal fat necrosis was found. It was concluded that a protective mechanism, consisting of plugging of the open duct by omentum, together with inhibition of pancreatic secretion, prevented intraabdominal spilling of pancreatic juice. If pancreatic secretion was stimulated by food or by cholinergic drugs, fat necrosis occurred. This experience suggested the study of other traumatic injuries of the pancreas.

EXPERIMENTS

Normal mongrel dogs, both males and females, weighing between 15 and 30 pounds were used. All traumatic procedures were performed under pentobarbital sodium anesthesia and sterile conditions. In the first group of 7 dogs an area of 1 to 2 square inches of the central portion of the pancreas was crushed completely across its width with Payr clamps, which were applied for a period of about 2 minutes. Subsequent bleeding was light and was controlled easily by compression. Ligation of 1 or 2 blood vessels was necessary in only a few instances. Three of the 7 dogs were starved for one day before and for 5 days after operation; they had access to water. The other 4 animals were fed before and after operation and received 3% dextrose solution instead of drinking water. Four of these dogs were sacrificed 2 weeks, two 3 weeks and one 4 weeks after operation. Immediate postmortem examination showed that in all dogs omentum was lightly adherent to the pancreas, that the pancreas was cirrhotic in its central, previously crushed portion, and that the rest of the gland was indurated. The pancreatic duct system was dilated in one dog. None of the dogs showed any fat necrosis.

In another group of 7 dogs a complete transverse tear across the pancreas was produced manually, by pulling apart 2 Allis clamps inserted into the central portion of the gland. This was followed by severe bleeding which could not be stopped by compression, necessitating the ligature of several bleeding vessels. Five of these dogs were starved before and after operation and 2 were fed pre- and postoperatively and given dextrose solution as the previous group. Two dogs were sacrificed after 3 weeks, two after 2 weeks and two after 1 week. One dog died with distemper 5 days after operation. In 2 dogs, one fed and one starved, a small number of preperitoneal and retro-peritoneal fat necroses were found. Otherwise no pathologic changes were present in any dog, except adhesions of omentum to the pancreas, a constricting scar where the pancreas had been torn, and varying degrees of induration of the rest of the gland. Dilatation of the pancreatic duct system was found in one dog.

None of the animals in either series of experiments appeared to be sick on the day after operation or later.

DISCUSSION

These experiments demonstrate that extensive crushing as well as tearing of the pancreas is well tolerated by the dog and is not followed by acute intraperitoneal processes, whether the animals were fed or starved before and after the operation. This is different from our previous experience with section of the pancreatic duct, where pre- or postoperative feeding seemed to be responsible for extensive intraperitoneal fat necrosis in a large number of dogs. An explanation for this difference may lie in the fact that in the present experiments the glandular tissue was damaged more severely than in the previous ones. This may have led to a drastic depression of external pancreatic secretion which, as in the earlier experiments, seems to be essential for survival of the animal.

The previous and the present series of experiments show that the pancreas in the dog is not an excessively delicate organ, but that it is rather resistant to traumatic injuries. This is in sharp contrast to the generally accepted characteristics of the pancreas of man.

The question poses itself whether or not the pancreas of man actually differs from the dog's pancreas in this respect, or whether the assumption of the extreme vulnerability of the human pancreas is not based on observations which our present knowledge and modern surgical technique may be able to overcome.

SUMMARY

Extensive crushing as well as tearing of the pancreas of the dog is not followed by apparent sickness or by acute intraperitoneal lesions such as fat necroses.

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The Function of the Hepatic Artery in the Dog

By

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and
A. C. SCOTT

TORONTO, CANADA

INTRODUCTION

That the blood supply to the liver is almost but not entirely conveyed by the portal vein is well-known today. Using the thermostromuhr method of measuring the blood flow through the hepatic artery and portal vein (Grab et al, 1929), it has been decided that the blood flow into the liver in the unanesthetized dog is roughly two-thirds of a cubic centimeter per gram per minute. Of this, the hepatic artery contributes about one-fifth of the total blood flow. However, it is appreciated as an extraordinary fact that whereas ligation of the portal vein, as in an Eck fistula, is without grave consequences to the organism, the ligation of the hepatic artery in the portal fissure beyond the last branches is invariably followed by a fatal outcome, usually within fifteen to fifty hours. This has been referred to, logically enough, as anemic necrosis of the liver. With the exception of the rat, these findings have been duplicated in many types of animals, including man, where in operations involving the billary apparatus the hepatic artery has been accidentally tied (Graham and Cannell, 1933). These facts are puzzling when one reads textbooks of histology concerning distribution of the hepatic artery. According to Maximow and Bloom the hepatic artery supplies the walls of the large veins and the intra-hepatic bile ducts, and only to a small extent does the hepatic artery nourish the parenchyma of the gland. Microscopic observations on the living animal by Wakin and Mann (1942) and also the experiments of Knisely et al (1948) indicate that the hepatic artery joins the radicals of the portal vein at the outer third of the hepatic lobule. There is nothing in the anatomy of this arrangement to explain the vital functions of the hepatic artery.

The question of the role of the hepatic artery was given a new twist by Wolbach and Saiki (1909). Employing extreme precautions against bacterial contamination they cultured the livers of 23 healthy dogs, and in 21 cases isolated a large spore-bearing anaerobe which grew with a marked formation of gas. Ellis and Dragstedt (1930) confirmed this finding and, according to them, the organism while not identical with the Welch bacillus is similar to it in some respects. It seemed to these authors that the fatal effects of leaving necrotic liver tissue in the peritoneal cavity are due to bacterial toxins. A reasonable inference is that the bacteria were phagocyted by the Kupffer cells, having originated in the digestive tract. To prove the point Ellis and Dragstedt removed the livers of pups by caesarian section and implanted these into the peritoneal cavities of adult dogs. They found that no serious effects resulted; such livers are uniformly sterile. Ellis and Dragstedt therefore claimed that the fatal effects of depriving the liver of its arterial blood supply were due to bacteria within the normal liver which proliferated when the blood supply was curtailed.

The conclusions of Ellis and Dragstedt did not remain uncontested. Boyce and McFetridge (1937) did an extensive study of autolysis of liver tissue in vivo. They concluded that death was due not to a generalized peritonitis but to the absorption of toxic products generated from liver tissue deprived of its circulation, and they stated that the negative experiment reported by Dragstedt and his workers, in which they used implanted foetal livers, was due to the fact that the livers were too small. They stated that even when they autoclaved the implanted livers death eventually resulted, but not invariably.

However, (and it might as well be stated here as later) the causes of death following the implantation of chunks of liver tissue need have no relationship to the cause of death following ligation of the hepatic artery. The literature on this problem has been more fully reviewed elsewhere (Markowitz, 1949). A brief bibliography of pertinent literature is included in this paper. We are more concerned here wth a physiological explanation of why, following the ligature of a small vessel like the hepatic artery, so large an organ as the liver undergoes a massive, gassy, perhaps stinking necrosis, when in point of fact the artery supplies only one-fifth of the total blood flow.

Narath (1916) did some notable early work on this subject. Repeating the work of his predecessors he showed that effective ligation of the hepatic artery in dogs was followed by the usual death of liver tissue, which he referred to as anemic necrosis. The experiments, which were interrupted by the First World War, deserve to be more widely quoted. He stated that when he anastomosed the hepatic artery to the portal vein, 3 out of 7 dogs survived, one living 12 and one 62 days. He reported no post-mortem data about the state of the anastmosis, only that Teichmann's fluid penetrated into the portal stream, which he took as evidence that the anastomosis, only that Teichmann's fluid penetrated into easily be displaced by this liquid forced in under pressure. He concluded that the necrosis of the liver is caused by lack of arterial blood and not as others believed that, not having arterial blood in the vasa vasorum, the branches of the portal vein thrombosed, resulting in massive hepatic necrosis.

In view of the importance of such a conclusion we have for 19 years, with interruptions owing to the Second World War, attempted, with ambiguous results, to repeat these experiments. (1) In the first place, doubling the blood flow through the portal vein by reverse Eck fistula does not prevent the effect of hepatic artery ligation. (2) We then attempted to anastomose the splenic artery to the splenic vein, together with effective ligature of the hepatic artery. As a rule, the

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junction underwent thrombosis and such animals promptly succumbed with a typical hepatic necrosis. (3) In a series of experiments we anastomosed side-to-side the aorta to the portal vein, thus arterializing its blood flow. Such an anastomosis is possible only in a few animals because owing to the angulation of the portal vein, fatal back pressure results in the intestines. (4) In a number of experiments we anastomosed the left renal artery to the splenic vein. (5) In two experiments we introduced arterial blood into the inferior vena cava by side-to-side anastomosis of the aorta to the vena cava, using the method of Eck fistula. The blood in the inferior vena cava was now shunted to the liver by a reverse Eck fistula, the hepatic artery being effectively tied. However, as a result of all these experiments we could never satisfy ourselves that the function of the hepatic artery could properly be substituted by arterializing the portal blood stream. Such operations are time consuming, and in a small experimental surgical laboratory such as ours, we doubt that the aseptic facilities are perfect, so during the last year we attempted to improve the post-operative convalescence of the dogs by injecting them with penicillin. During the past year a surprising number of animals withstood effective ligation of the hepatic artery and arterialization of the portal vein. It appeared at last that our researches were confirming Narath's views, until we post-mortemed the animals to examine the operative site. We then found that invariable thrombosis had occurred at the vascular union; that no arterial blood was entering the portal vein; that the hepatic artery was effectively ligated; that the liver, in the gross at any rate, was not much altered; and that the animal had survived an operation which totally deprived the liver of arterial blood. Such a conclusion was hard to understand. At first it appeared to us that possibly the liver could adapt itself to a slowly diminishing tension of oxygen, such as would occur during the gradual thrombosis of an arterio-portal anastomosis. However, there was a faint possibility that the pencillin might have played a part in the results. To control this possibility a series of experiments was performed in which half the dogs were subjected to effective ligation of the hepatic artery with no other post-operative treatment, while the other half were subjected to similar treatment, but were given penicillin post-operatively. We found unexpectedly that most of the latter recovered. A series of experiments was then undertaken in which the hepatic artery was ligated and massive doses of penicillin were given intra-peritoneally and subcutaneously. We thus confirmed the discovery that so-called anemic necrosis of the liver can nearly always be prevented, barring such post-operative accidents as perforation of the gall bladder with bile peritonitis. We have seldom had a dog die of "anemic" hepatic necrosis that was given large doses of penicillin. Whenever we wish to produce an animal with a liver that is supplied only by the portal vein, we tie the hepatic artery as described below and give the animal large doses of penicillin intra-peritoneally and subcutaneously for 10 days, and we can predict with confidence that the animal will recover and will be normal looking when the treatment is discontinued for at least as long as three months.

EXPERIMENTAL METHODS AND PROTOCOLS

Since ligature of the hepatic artery almost necessarily involves the nutrient vessel to the gall bladder, with resultant gangrene of the vesicle, one of the first questions in this research was whether to remove or not to remove it. We soon found that the mortality following this procedure was slightly greater than if the organ were left in place, for the animal now had two operative procedures from which to recover instead of one. Accordingly, in most experiments the gall bladder was left in situ, and we hoped that the defensive forces of the animal would wall off the gangrenous process, a hope that was realized. In the great majority of the experiments when the animal came to autopsy it was found that the gall bladder had disappeared, and that the area was occupied by a mass of dense adhesions. In typical experiments the gall bladder area was adherent to the convexity of the diaphragm, or the liver lobes had adhered around it. On section this gangrenous area had become fibrosed and the examiner's knife even gave the impression that the wall had become calcified. When this localizing process had failed, as occasionally happened, the animal developed a bile peritonitis to which it succumbed.

In the dog cholecystectomy does not always prevent bile peritonitis since occasionally a hepatic duct empties directly into the gall bladder which upon removal leaves a raw area into which bile discharges. In the human being this is obviated by placing a drain in the gall bladder fossa. In dogs this is impractical because the dogs remove the drain.

I. In one experiment (No. 14) in which the hepatic artery and all the branches were tied as usual, cholecystectomy was performed, leaving a small stump of cystic duct. Two hundred thousand units of penicillin were given intra-peritoneally. The next day the dog was dyspnoeic. He was given 100,000 units of penicillin intra-peritoneally and 100,000 units intramuscularly. Next day the animal died during the night. At autopsy about 100 c.c. of blood were found in the abdominal cavity. The liver looked comparatively normal. There were a few blotchy areas of liver tissue but in general the organ was normal in size, and was not spongy, soft or necrotic. The lungs were bluish-red in color, possibly pneumonic. Death was due to bile peritonitis from a leakage of bile from the cystic duct.

A typical protocol concerning effective ligation of the hepatic artery is as follows:

II. (No. 15) A brown and white collie weighing 17.7 kilograms was operated upon under nembutal anesthesia. Cholecystectomy was performed. The hepatic artery and all the branches were tied in the usual manner. In practice, this involves ligature of the gastroduodenal, right gastric and other branches of the artery before its bifurcation into right and left hepatic artery proper. About 5 or 6 ligatures ordinarily are tied with

linen, and these extended into the portal fissure.

We early found it wise to alter the normal relation of the hepatic artery to the portal vein, to get proper exposure. Normally the artery exists as a pulsating loop surrounded by nerve fibres to the right of the vein. This was tied, nerves and all, and leaving the tie long, the vessel was pulled to the left of the vein by creating a hiatus above the last tributary of the portal vein. A hemostat could here be insinuated in the direction of the artery, the ties were seized and the vessel transposed forcibly. This maneuver made subsequent dissection easy and safe.

No pencillin was given. Twenty-four hours later the animal was found dead in its cage, having survived less than twenty-four hours. At autopsy the abdomen was distended, the skin was slightly discolored. When an incision was made into the peritoneal cavity, a puff of foul smelling gas was emitted. The liver was necrotic, unchanged in size and spongy to feel. On section the necrosis was uniform. All these terrific changes had taken place in one day.

III. (No. 22) A similar control experiment was done, with the difference that the gall bladder was not removed and the animal was given 200,000 units of penicillin intra-peritoneally and 500,000 units intra-muscularly. The animal was anesthetized twenty-four hours later and examined. The liver seemed entirely normal in the gross, and sections were taken and given to our colleague, Dr. W. S. Hartroft. The findings were so entirely normal that he rightly doubted the efficacy of the ligatures. As a result, subsequently when specimens were submitted to him for examination the structures in the portal fissure were removed in one mass so that he would be able to confirm or not the occlusion of the hepatic artery extending to the portal fissure.

IV. (No. 19) Jan. 12/49. Black and white terrier, weight 14.5 kilograms. The gall bladder had an extra cystic duct which was cut accidentally. There was some leakage of the bile. This was controlled by ligature. The animal was given 200,000 units of penicillin intra-peritoneally and 200,000 units of penicillin procaine monosterate intra-muscularly.

Jan. 13. 200,000 units of penicillin procaine intra-muscularly.

Jan. 14. Ditto; the animal ate bread and milk but not ravenously.

Jan. 16. Ditto.

Jan. 20. Dog not eating. Stitches removed. Subcutaneous abscess at the top of the incision drained. Looked bile-stained. Given 300,000 units procaine penicillin monostearate.

Jan. 21. Dog died during night.

At autopsy there were post-mortem changes in the stomach, intestines, spleen, etc. The liver appeared normal in size. It was neither soft nor necrotic. There was no foul smelling gas. The gall bladder was deeply bile-stained and there was a moderate amount of reddish-yellow bile-stained fluid in the peritoneal cavity. Sections of a fairly normal looking liver and of the gall bladder bed were taken. It was concluded that the animal died from bile peritonitis resulting from the leakage of bile.

The following are two parallel protocols, one involving ligation of the hepatic artery with penicillin and one without.

V. (No. 22) Feb. 10/49. (Mentioned in No. III). Black and white terrier, weight 12.9 kilograms. The hepatic artery was tied in the usual manner. 200,000 units of penicillin were given intra-peritoneally and 300,000 units of penicillin procaine monostearate intra-muscularly.

Feb. 11. The dog was anesthetized. Laparotomy was performed. The liver looked normal except for one or two blotchy dark areas. Culture was taken from the portal vein, vena cava and liver tissue. Smears of liver tissue and peritoneal cavity were taken. Sections were removed from the liver, gall bladder, spleen, pancreas and kidney. The dog was killed. Histologically the liver showed minor changes on which Hartroft will report.

VI. (No. 23) Feb. 10/49. On the same morning a sand-colored hound, weight 13 kilograms, was operated upon. The hepatic artery was tied in the usual manner and the animal given no pencillin.

Feb. 11. The dog was anesthetized and opened up. The liver was dark in color and in some areas was necrotic and spongy. There was a moderate amount of bloody fluid in the peritoneal cavity. The omentum and the peritoneum were much thickened. The gall bladder wall looked thin and necrotic. There was a foul odor as noted in former autopsies, even though the dog was still alive. Smears, cultures and specimens were taken as for dog No. 22. Histologically the liver was totally necrotic with millions of bacteria everywhere.

VII. We have observed the effects of penicillin after ligating the hepatic artery for as long as three months post-operatively. In one experiment the dog was deliberately sacrificed three months after operation to study what had happened and to verify the fact that the ligatures were still effective. What remained of the gall bladder was a thickened, fibrous, ligamentous mass attached to the diaphragm at its point of origin from the anterior abdominal wall. It was surprising that in gross the liver looked rather normal though possibly reduced in size.

VIII. Another dog that survived approximately three months was found dead in its cage one morning. At autopsy it was found that a loop of bowel had been transformed into a volvulus with fatal intestinal construction. The liver, though possibly slighty reduced in size, was entirely normal in the gross. What remained of the gall bladder was a small, fibrous, ligamentous, possibly calcareous mass of tissue firmly adhered to the surrounding liver lobes. On section, it gave a gritty sensation to the knife.

Histologically our colleague Hartroft reported several surprising features. (1) Dog No. 23, treated with

penicillin, as stated above had the hepatic artery tied 24 hours before it was sacrificed for examination. There was so little change that Hartroft questioned the efficacy of the ligatures. For example he found that the hepatic arterioles contained unclotted blood, and the bile ducts had an intact epithelial lining. Because of this, in the future, we also submitted our ligated hepatic artery for examination. As a matter of fact, in the past three years we do not recall an instance in which a dog, without penicillin, survived our method of tying the vessel. (2) The liver of dogs untreated with penicillin showed massive total necrosis. (3) Overwhelming numbers of bacteria, nearly all spore. bearing bacilli were everywhere present in the necrotic tissue, its blood vessels and bile ducts. Also the pancreas and kidney showed these in multitudes.

DISCUSSION

Certain novelty shops in Toronto have for sale an egregious item known as the jackass barometer. It is chiefly in demand among such embittered intellectuals as comprise the vanguard of unreason. It consists of a picture of a jackass on a flat plane, obviously saying "hee-haw" and with a piece of real string protruding from its rear end, representing the animal's tail. This barometer is meant to be hung out of the philosopher's window to indicate weather conditions. It is stated in the accompanying instructions that when the string waves, it is windy; when the string is wet, it is raining; and when the string waves and is wet, it is stormy. This instrument (who knows?) might have delighted Lord Bacon, the father, if not the mother, of the inductive method, and the reasoning employed in our paper is about as direct. Thus, an antibiotic completely prevents the hepatic necrosis normally consequent upon tying the hepatic artery; therefore the necrosis is bacterial in nature, a fact which microscopic sections of the necrosed liver confirm. The necrosis follows ligature of the arterial supply to the liver and does not follow ligature of the venous trunk; therefore the bacterial infection is anaerobic, again a fact which bacteriological studies have frequently disclosed. In fact, the gangrene of the liver thus produced turns out to be a true gas-gangrene, which may reasonably be compared with the corresponding gas-gangrene of the leg in a wounded soldier. In the days before penicillin we attempted to elucidate the function of the hepatic artery by adding arterial blood to the portal vein. We do not in this paper intend to present evidence regarding the efficacy of preventing such necrosis by arterio-portal anastomosis. In the meantime a wholly unexpected bacteriological tool, strictly the product of time and induction, has illuminated a mysterious corner of physiology. The immediate urgent function of the hepatic artery is to keep the oxygen tension of the liver sufficiently high to discourage proliferation of anaerobic bacteria. The O_2 tension of arterial blood, 72 mm. Hg, is present at an atmosphere above the earth 6.5 kilometers high; that of mixed venous blood, 40 mm. Hg, represents an O_2 tension in an atmosphere 10.5 kilometers high. In the human pulmonary alveoli, this would very roughly represent the difference in tension between Pike's Peak and Mount Everest.

This function of the hepatic artery is a new type of homeostasis and is a curious piece of evolution in the elaboration of higher organisms. As to when the hepatic artery first appears in the animal scale we have no data. It would involve not only a study of the arterial tree, but of a symbiosis between the liver and organisms of the Welsh bacillus type, their natural occurrence in the gastro-intestinal tract, and their sub-lethal suppression by sufficiently high oxygen tension. Limulus polyphemus, the king crab, is a very ancient species. We should be glad to hear if its liver is serviced by a hepatic artery.

SUMMARY

Our experiments, using penicillin, settle a current controversy in favor of Dragstedt and his school, who maintain that the liver normally houses an obligatory anaerobe which proliferates and fills the liver when arterial blood is no longer offered to the organ. By means of a few doses of penicillin it is possible almost regularly to tie the artery to the liver with apparently indefinite survival of the dogs. The physiological properties of such animals will be reported in future papers.

These experiments owe much to the critical supervision of the Head of the Department, Dr. C. H. Best.

Dr. E. A. Ryan, Dr. J. F. Murray and Dr. L. S. Davies will be glad to hear that the many hours they spent with us early in the problem at last bore fruit

Dr. Stanley Hartroft is responsible for the post-mortem examinations, and he will report his findings later.

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Anoxia and the Liver with Special Reference to Shock and Chronic Malnutrition

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The elucidation of the etiology of cirrhosis and of steatosis of the liver has claimed the attention of the overwhelming number of investigators interested in hepatic disease in different parts of the world. A third type of liver reaction, characterized by the appearance of fat-free vacuoles and well known to those having had occasion to use the chlorinated hydrocarbons experimentally in rats, is usually dismissed casually as hydropic degeneration without any further attention.

During the last six years, renewed interest in the vacuolar type of reaction was aroused mainly because of its appearance frequently in the liver and other organs of airmen dying from acute anoxia during combat. Trowell (1946) has attemped to ascertain the various factors involved in the genesis of this phenomenon by resorting to experimental techniques applied to rats and other laboratory animals. While the suggestion that congestion of the liver in anoxia increases the permeabiliy of the sinusoids and this permits the passage of fluid into the liver cell is not entirely acceptable, Trowell nevertheless, is to be greatly commended for suggesting that all types of vacuolated cells may have a common pathogenesis. He included within the same category of vacuoles those appearing after carbon tetrachloride poisoning, the administration of adrenalin, as well as those recored by Mallory (1901) and Pappenheimer and Hawthorne (1936) in the livers of human subjects coming to post-mortem examinatons and dying from a variety of causes. He suggested that perhaps the vacuolated cells seen in livers of protein-deficient animals also might be similar to those observed in the livers of individuals dying from anoxia

In a previous study, we have drawn attention to water-clear cells in the livers of malnourished subjects recovering from an acute attack of pellagra (Gillman and Gillman, 1945). These vacuolated cells, particularly, obtruded themselves during a survey of our large series of livers of individuals dying from a variety of different causes. These vacuoles were especially numerous after fatal haemorrhage, multiple injuries, carbon monoxide, prussic acid poisoning and in the livers of many still-born infants.

After a fatal haemorrhage, the presence in the liver of cells resembling plant-cells and virtually indistinguishable from those described by Elman and Heifitz (1941) and Elman et al (1943) in their protein-deficient dogs and rats, made it quite clear that the hydropic changes was a manifestation of a very special type of metabolism and not merely of an altered permeability of the intralobular sinusoids. This was all the more possible because similar vacuolated cells have been described in skeletal and cardiac muscle (Kritzler, 1944). It soon became clear that both the vacuolated and plant-like cells were similar types of reaction, more especially because they are often found associated in the same slice of liver.

The abundance of material made it obligatory for us to discover the several stages in the formation of vacuolated and of the plant-like cells, recording wherever the occasion permitted the behaviour of the other common cytoplasmic inclusions, such as fat, chromidial substance, glycogen and mitochondria.

Thereafter, it seemed desirable to ascertain the extent to which one kind of anoxia permitted the development of vacuoles more than another. The large number of necropsies performed annually at the Medico-Legal Laboratories serving the cosmopolitan city of Johannesburg provided a very rich material for such a kind of investigation.

Since the several conditions which led to the death of subjects whose livers formed the basis of this study could in different circumstances, lead to shock, a correlation was justified between morphological findings in human subjects and the physiological observations made

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on the livers and other tissues of shocked animals. This correlation was greatly facilitated by the splendid observations made during the recent war.

While the limitations of this type of correlation were fully appreciated, nevertheless, we still feel that such a correlation might assist in providing perspective on the relationship of the liver in such shock-states as might be followed by recovery or which might eventually lead to death.

It is also our purpose through this type of comparison, to disclose that the several splendid investigations into the biochemical changes occurring in the blood and tissues induced in different ways remain incomplete as long as such investigations are not supported by histological examination of the various tissues of the shocked animal.

Reactions undoubtedly occur first at the chemical level and sometimes such reactions may be translated rapidly through successive levels until they may become observable at the morphological level. This certainly happen in the case of the vacuolar reaction. As will be shown later in this study, vacuolated and plant-like cells are frequently seen in the liver of subjects dying from acute shock. It would therefore seem that examination of the several factors involved in this type of reaction might conceivably aid in disclosing several links in the chain of events which in some circumstances may be associated with the development of acute shock.

Our original purpose in undertaking this study of the vacuolated cell and its relation to anoxia was determined mainly by our interest in the behavior of the liver in various forms of chronic malnutrition. After a consideration of the relevant evidence it is our intention to put forward the view that some kinds of dietary stimuli may lead to reactions in the liver which are simlar to those observed in anoxia and in shock. This view we opine may serve to emphasize that seemingly unrelated stimuli may eventually lead to a similar disturbance in a fundamental physiological regulation and this in turn may have a common morphological end result. While it is essential to observe the several local events which eventually lead to a particular variety of injury to an organ, it is equally essential to appreciate that such a particular injury may represent a disturbance of a common physiological regulation. The several different stimuli which eventually culminate in the disturbance of a physiological regulation may then become a useful technique or indicator for the elucidation of the factors immediately or remotely responsible for the maintenance of a particular regulation. It is in this way that we propose to examine the significance of the vacuolated and plant-like cell in livers of human subjects suffering from malnutrition and those dying from a variety of different causes.

MATERIAL AND METHODS

The 275 livers which formed the basis of this investigation were derived from two sources. The majority (188) were obtained from European and African subjects dying unnaturally and therefore coming for examination to the Medico-Legal Laboratories, Johannesburg. The overwhelming number were African males who died as a result of injuries sustained in industrial mishaps, brawls or street accidents. Carbon monoxide poisoning is particularly common in Johannesburg, where, during the winter months, coal braziers are taken into poorly ventilated rooms. Deaths from prussic acid poisoning were the result of suicide or accidents during fumigation.

By virtue of a special privilege extended by the Minister of Education to Professor Raymond A. Dart, we have been able to accumulate tissues from African subjects executed for murder and other crimes. In this way, 87 livers were accumulated during the last 18 years The livers from the latter cases were obtained usually 20 minutes of death.

Tissues were fixed wherever possible in several different ways for cytological and other investigations. Frozen sections were cut from all livers and these were stained for fat. As a routine, haematoxylin and eosin sections were prepared from formalin-fixed tissue. All livers were stained for iron pigment. A selected series of livers were stained for mitochondria by Dry's (1945) modification of Altmann's aniline fuchsin-methyl green technique, for glycogen with Best's carmine, and for chromidial substance with pyronin-methyl green. In addition, selected livers were stained with Pasini's mixture and a modification thereof found useful for the purpose (Gatenby and Painter, 1937).

It should be strongly emphasized that unless vacuoles in the liver cell contain the curious inclusion body or rodlet, it may be extremely difficult in sections prepared from paraffin-embedded tissues to decide whether or not a particular vacuole contains fat. For this reason frozen sections stained for fat were always prepared when vacuoles were seen in the haematoxylin and eosin sections. It should be added that a cell rich in glycogen may sometimes resemble a plant-like cell and therefore the additional precaution was taken of staining alcohol-fixed tissues with Best's carmine.

PATTERN OF REACTION OF THE LIVER IN ACUTE ANOXIC DEATHS

In the overwhelming number of acute deaths listed in Table 1, the liver usually exhibited one or both of two patterns of reaction. In the first, the hepatic cell develops one or more cytoplasmic vacuoles and hence may be conveniently named the *"vacuolar pattern of reaction"* (Fig. 1). In the second, the cytoplasm loses its stainable contents to become optically empty, while the nucleus, lodged near the centre of the cell, is seemingly suspended by a number of widely separated, delicate cytoplasmic threads from the apparently thickened cell membrane. The resemblance to a plant cell, even when the cytoplasm contains a sparse quantity of granules embedded in an abundant amount of ground substance, is so unmistakable that we have suggested the name of *plant-like cell pattern of reaction* (Fig. 2 to Fig. 8).

The genesis and fate of the vacuole.

The non-fat, non-glycogen-containing, fully-formed vacuole has been observed in the liver by several investigators dating back to Mallory's observations (1901). Pappenheimer and Hawthorne (1936) have also described similar vacuoles in the livers of human subjects dying from a variety of causes. These two investigators were particularly intrigued by the granular rodlet or delicate meshwork usually seen in this vacuole. They did not attempt to examine the genesis of either the vacuole or the peculiar inclusion body. During the recent war Mueller and Rotter (1942) recorded the presence of fat-free vacuoles, either optically empty or filled partially with refractile granules staining lighty with eosin, in the livers of four airmen who died from high-altitude anoxia. Similar observations were made by Buchner (1942), and Pichotka (1942). Pichotka observed these vacuoles in guinea-pigs subjected to reduced supplies of oxygen at normal pressure, while Mueller and Rotter (1942) described them in the liver cells of four airmen, dying from high-altitude anoxia, as big round or polyhedral fat-free vacuoles, optically empty or partially filled with refractile granules staining faintly with eosin. In the former instance, the vacuole was lined by a crescentic rim of slightly acidophilic homogeneous material. Hesse (1942) apparently found identical vacuoles, especially in livers of drowned or suffocated individuals. Similar vacuoles were observed by Ladewig (1943) in the livers of guinea-pigs exposed to chloroform vapour for three to five hours.

Kritzler (1944) gave a full description of the vacuoles in the livers and other organs of 27 airmen dying from high-altitude anoxia and not suffering any external injury. In Kritzler's cases, the vacuoles were also found in the sarcoplasm of cardiac muscle where they varied in size from 2 to 12 micra and in number from 1 to 15. The large vacuoles usually encroached on the nucleus, single or double concavities or pronounced crescentic deformities usually resulted. The nuclei appeared to indent the vacuoles. The majority of the vacuoles usually contained a single centrally or excentrically located particle about 1 micron or less in diameter in the case of the heart vacuoles and, slightly larger, in those of the liver cells. These inclusions were about the same size in the large as in the small vacuoles. Kritzler also observed similar cytoplasmic structures in the pancreas, in eosinophilic cells of the pituitary and in cells of the stomach while in the kidneys he recorded a peculiar watery swelling, the endothelial cells of the capillaries, despite the tight packing of the corpuscles, bulged into the lumen, almost touching those of the opposite wall. In order to discover whether appearance of vacuoles was specific to anoxia, Kritzler investigated the livers and the hearts in 14 cases dying from other causes. In these cases, vacuoles were often found in the heart, though in four of five cases of carbon monoxide poisoning, vacuoles were also found in the liver. Kritzler affirmed that vacuolar changes in the cell were not affected by the length of time intervening from the time of death and the performance of the necropsy.

The most comprehensive account of the structure of the vacuole and the factors determining its formation has been provided by Trowell (1946), particularly as observed in the livers of rats, rabbits, guinea-pigs and monkeys. By much painstaking experimentation Trowell was led to conclude that the vacuoles were the consequence of intense congestion of the liver associated with acute anoxia.

In summarizing the literature, it would appear that the vacuole has the following characteristics: (1) the wall may be a little darker than the enclosed contents (Trowell); it may be in the form of a faintly staining eosinophilic rim (Rotter and Mueller, Pichotka); (2) it is optically empty (Trowell, Kritzler) or it may contain fine translucent or faintly eosinophilic granules (Rotter and Mueller). Despite his repeatedly expressed opinion, Trowell states that the contents sometimes contained a homogeneous material which stained lightly with cytoplasmic dyes, pale red with eosin, grey with iron haematoxylin, pale bluish-grey with haemalum — aurantia — aniline blue mixture used by Marshall and Trowell (1943). According to Trowell these staining reactions resembled those of plasma protein as seen by comparison with stainable contents of adjacent blood vessels; (3) the vacuole may contain a spherical, thread-like or rod-like inclusion (Mallory, Pappenheimer and

FIG. 1. A cluster of liver cells showing punched out, fat-free, glycogen-free vacuoles near a central vein; from a case of prussic acid poisoning. X 325, stained with hæmatoxylin and eosin (H+E).

FIG. 2. A mass of plant-like cells extending from the central vein of one lobule to the central vein of the next lobule. Note how the entire segment of one lobule is affected and that plant-like cells are found close to the portal tracts (a;b). X 50, stained with H+E. Case of traumatic asphyxia

FIG. 3. High power study of portion of Fig. 3 to show the morphology of the plant like cell. The portal tract seen in the figure is the one shown at a in Fig. 2. Note the absence of congestion and the great enlargement of the individual cell as compared with Fig. 1. X 325.

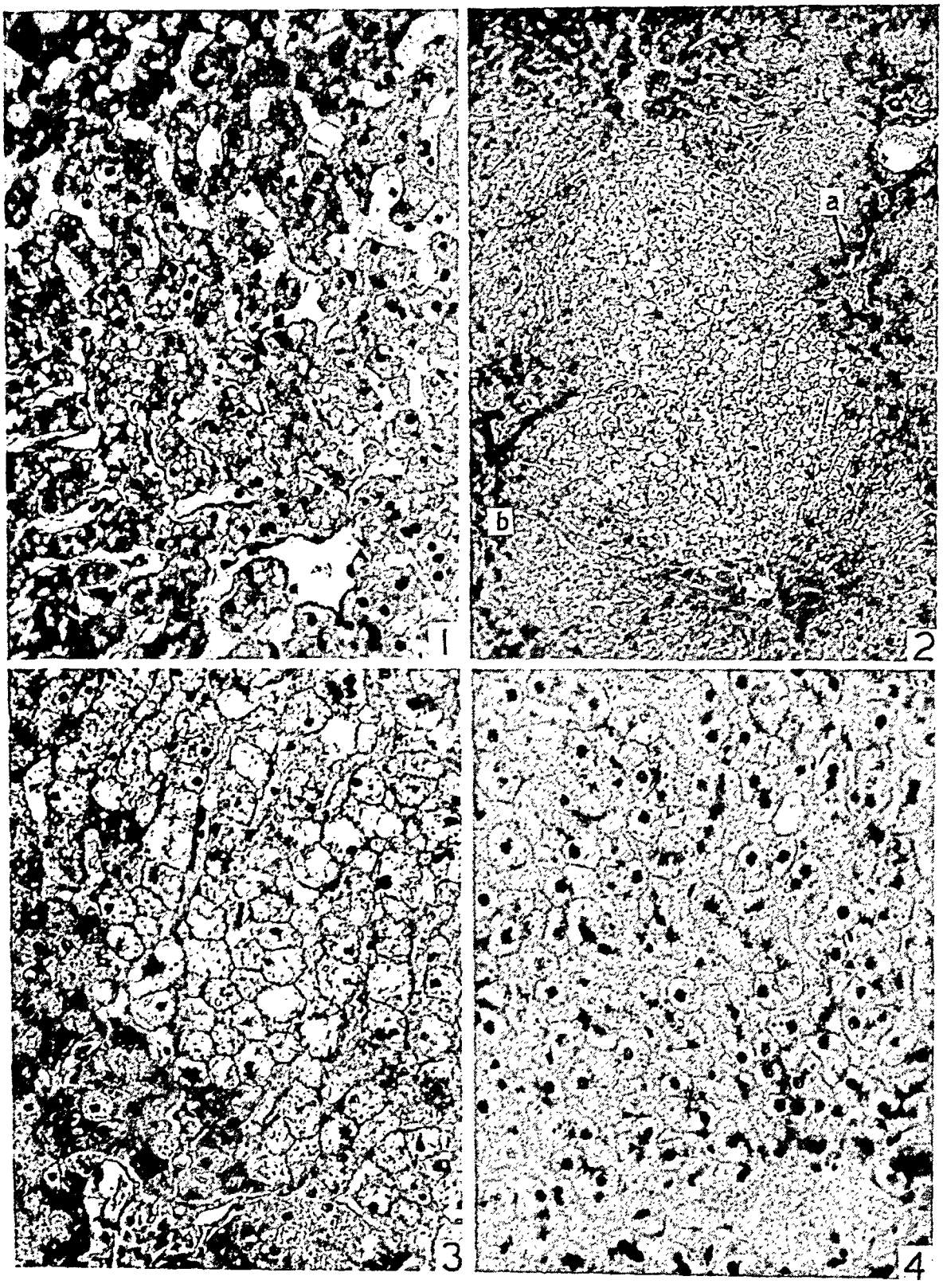
FIG. 4. The liver showing plant-like cells after a rapidly fatal hæmorrhage. X 325.

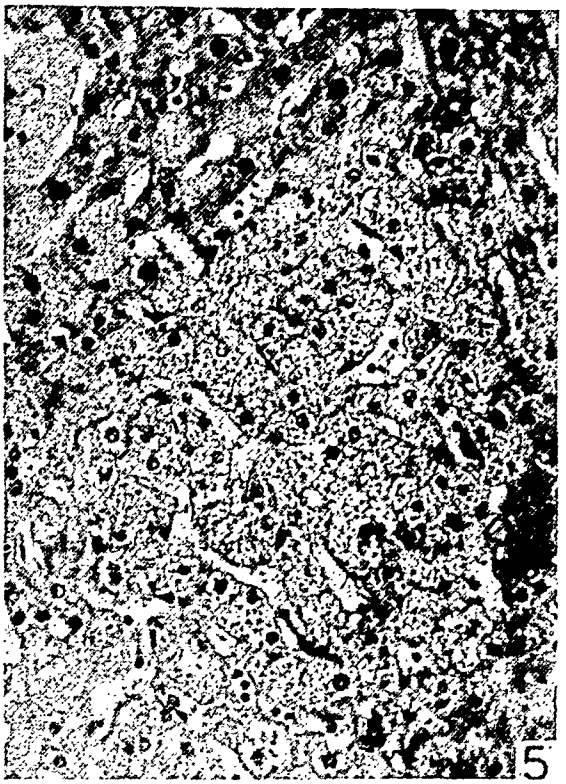
FIG. 5. Another region of the same liver as depicted in Fig. 2, to show rarefaction of cytoplasm and an increase of non-stainable ground substance; this is the early stage in the formation of plant-like cells. X 325, tained with H+E.

FIG. 6. Plant-like cells near portal tract and numerous enlarged chromatolytic nuclei as compared with hyperchromatic nuclei near the top and bottom of picture. X 325. A case of fatal hæmorrhage.

FIG. 7. Plant-like cells containing variable-sized masses of colloidal material; some of these masses are about the size of the nucleus (a), some half-filled the cell (c); and optically empty cell (b). X 650, stained with Pasini's mixture. From a case suffering fatal injuries.

FIG. 8. Mitochondrial preparation of a mass of plant-like cells in the liver of a subject after hanging. Note the distribution of mitochondria particularly under the cell membrane; for the rest the cytoplasm is filled with non-stainable material; glycogen was not present in these liver cells. Compare with Fig. 3. Such types of cells are frequently seen in the livers of pellagrins. X 850, stained with Dry's modification of Altmanns aniline fuchsin-methyl green technique.


a
b
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2
3
4



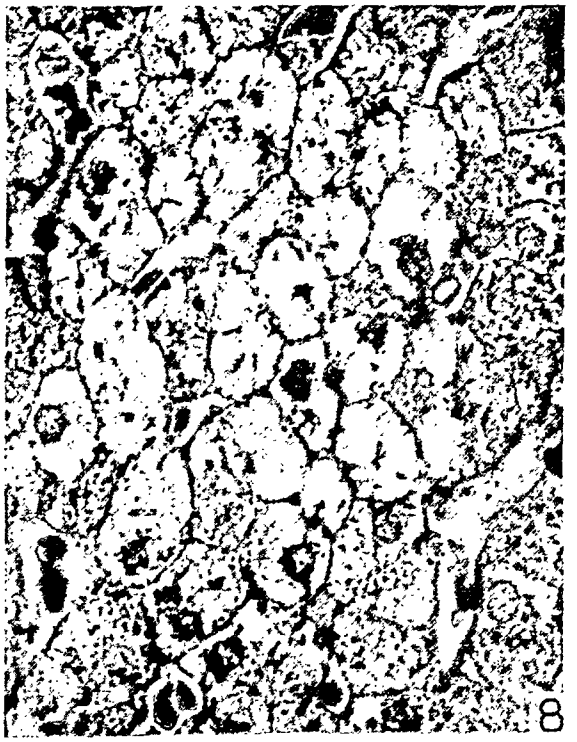
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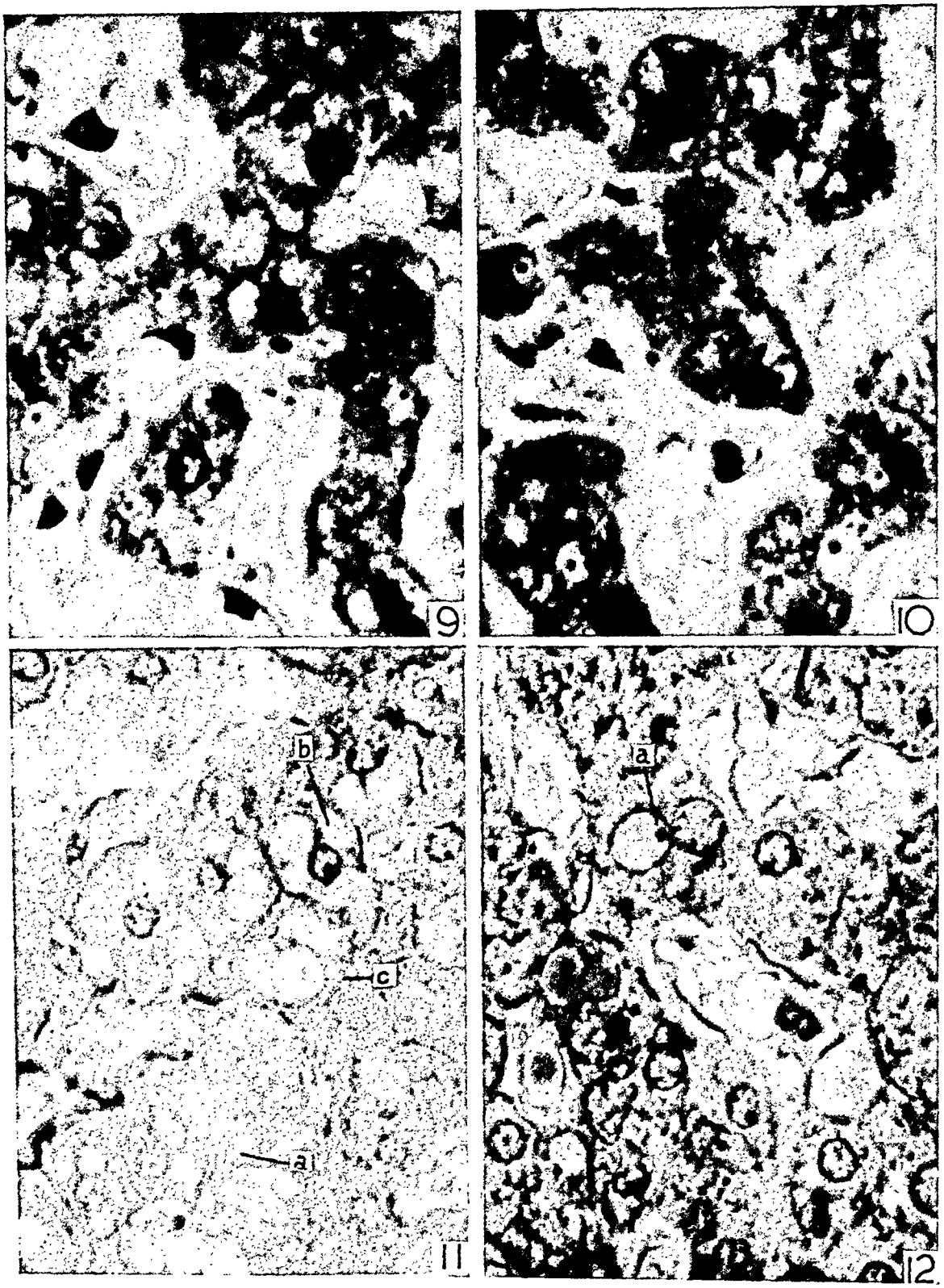
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13



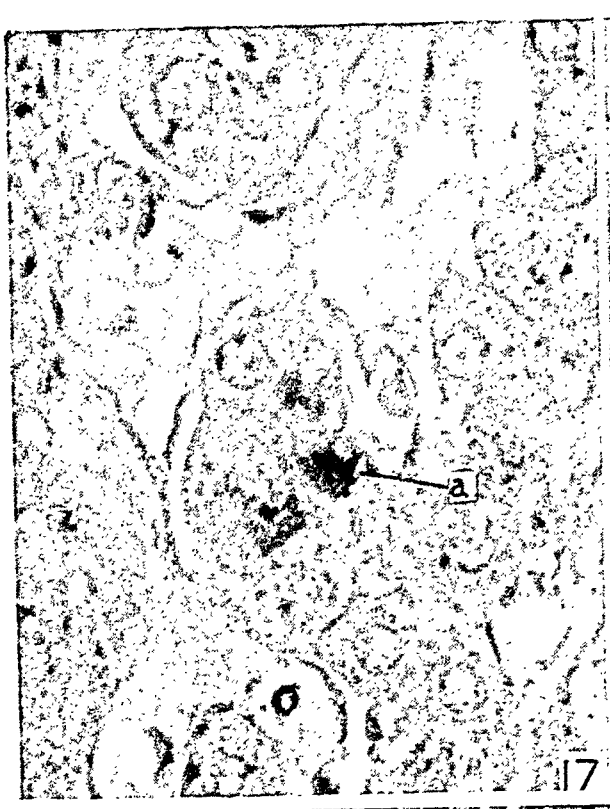
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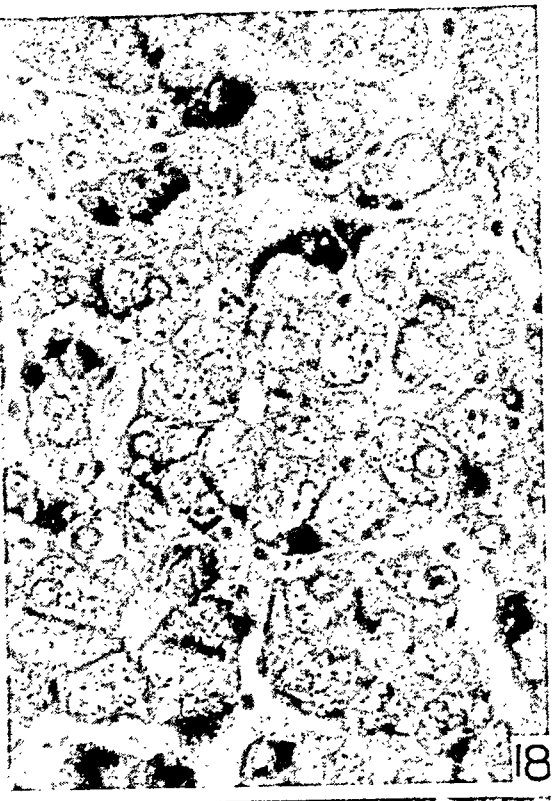
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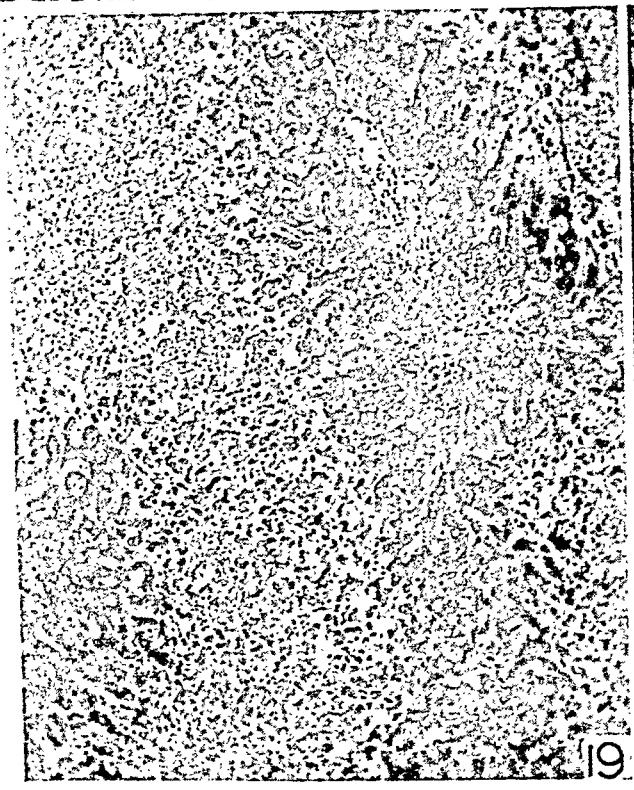
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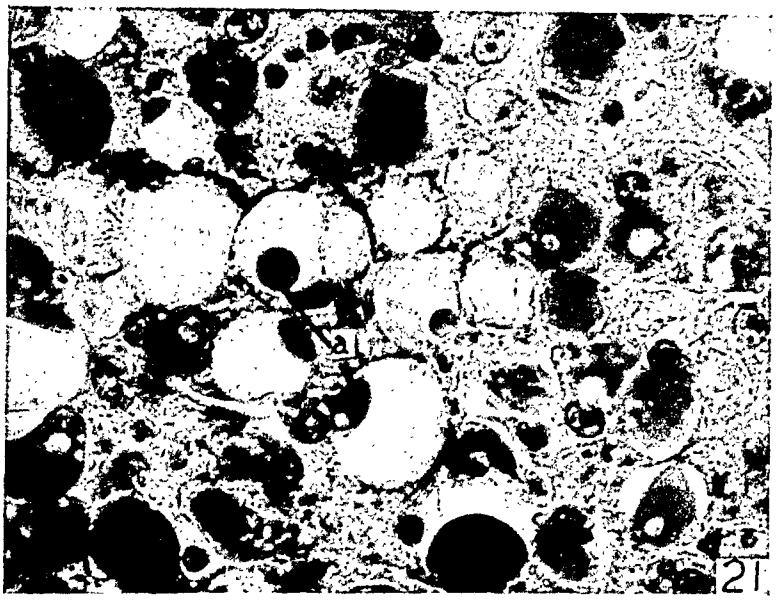
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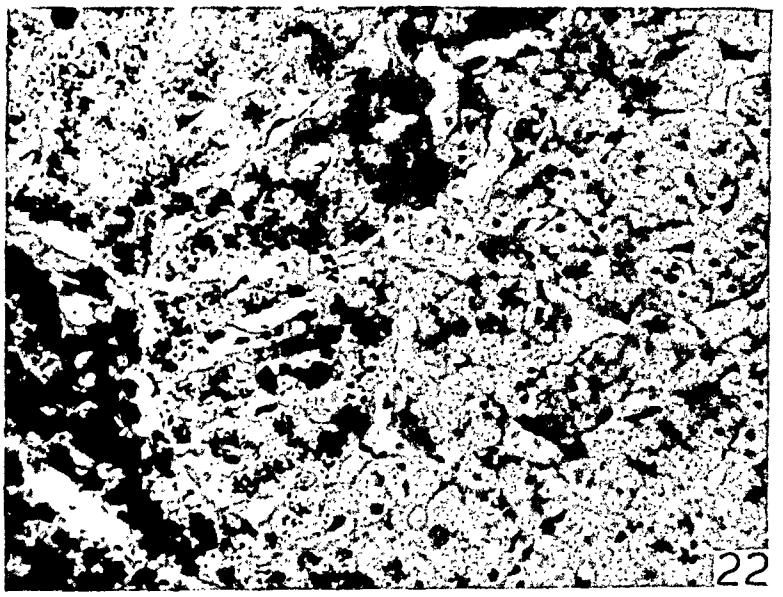


19



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a
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22

Hawthorne, Rotter and Mueller, and Kritzler); (4) the vacuoles contain neither fat nor glycogen; (5) the glycogen, mitochondria and ribonucleic acid aggregates show no particular orientation nor is there any change in these components as compared with normal cells (Trowell); (6) the vacuole is seen in the living cell and is not the product of autolysis; in teased fresh liver the vacuole maintains its integrity after rupture of the cell membrane (Trowell).

If the significance of these vacuoles in the cells of the liver and of other organs in anoxic deaths is to be understood, then clearly the events in the cell leading up to formation of the vacuole need to be more clearly established. A knowledge of the morphogenesis will also serve to remove some of the discrepancies in the literature pertaining to the structure of the vacuole, especially as cytological investigations are often presented without reference to the dynamics of metabolism of the cell immediately preceding death.

A given cytoplasmic inclusion may quite easily assume widely divergent morphologies at short intervals of time. These divergences may be sufficiently well-marked to cause some confusion when not related to the developmental history of the cytoplasmic inclusion in question. Unfortunately, in fixed and stained preparations the morphogenesis of the vacuole, like that of any other inclusion, can only be pieced together and therefore it is not always possible to be certain that events are arranged in the same serial order as they occur in the living cell. Nevertheless, the reconstruction of the stages of the morphogenesis of the vacuole even in section does serve to emphasize the importance of the dynamics of the process and also relates the events leading to the formation of the vacuole with corresponding effects on the other cytoplasmic structures.

In haematoxylin and eosin stained sections of the liver, the vacuoles are easily recognized by their sharp contours emphasized by the more intensely coloured cytoplasm (Fig. 1). The small or large, round or oval punched-out vacuoles are to be found in any part of the cell (Figs 9 and 10). Sometimes they appear to be more numerous near the biliary pole, while at other times or in different cells they congregate near the sinusoidal pole or around the nucleus where they are often disposed in the form of a crescent. In this region the vacuoles may indent the nucleus and more usually the nucleus deforms the vacuole. When numerous, the contiguous walls of adjacent vacuoles may disappear and the fused vacuoles may form a variety of different patterns (Fig. 11).

All investigators are agreed that the vacuoles may be optically empty, and with the exception of Trowell are also agreed that sometimes a prominent granule may be seen lying in the centre or towards the periphery of the vacuole. The granule or rodlet is not a constant feature in our series of livers, although they were observed consistently in some livers (Fig. 9, 10, 12, 14) and particularly in the livers of still-born infants. When the vacuole and its contained granule indented the nucleus slightly, the picture was almost indistinguishable from that observed in the young spermatid with its large optically empty acrosomal vesicle and the acrosomal granule (Fig. 9). The appearance of the granule (Fig. 12,a) or rodlet (Fig. 13,b) within the vacuole in the liver cell is conditional apparently on some special type of metabolism which does not prevail in all liver cells at the same time.

The wall of the vacuole in haematoxylin and eosin sections is often very sharp and may even be intensely eosinophilic. In some instances the wall is less well defined and a thin eosinophilic film extends irregularly into the empty space. Occasionally the wall is so indistinct that the vacuole is represented by a localized rarefaction in the cytoplasm. While on casual examination, even under oil immersion objective, the punched out vacuoles appear to be optically empty, careful manipulation of the light often reveals the presence of small non-staining granules or extremely small vacuoles tightly packed together and completely filling the main vacuole. As will be more fully indicated, the contents of these vacuoles can only be seen to advantage when stained with Pasini's mixture or in Helly-osmic-fixed tissue stained with Dry's modification of Altmann's aniline fuchsin-methyl green technique. In haematoxylin and eosin-stained sections, frequently one of the granules in the vacuole appeared to be larger and exhibited a greater affinity for eosin than did the others. This special granule is doubtless the precursor of the granular or rod-like inclusion body. However, it should be mentioned that not all vacuoles contained these numerous fine granules and consequently appeared to be optically empty. This observation was confirmed later with the aid of special techniques.

In haematoxylin and eosin preparations two main types of vacuoles are therefore to be seen even in one field; these are the vacuole filled with discrete particles and an optically empty vacuole. Moreover, all transitions from the one to the other may be recognized.

The vacuole can assume a variety of appearances, although the most striking one is characterized by a rather sharply-defined eosinophilic wall enclosing an optically "empty" space in which a spherical, intensely eosinophilic body is lodged (Figs. 9 and 10). Only Buchner and his associates previously recognized the presence of masses of minute granules or tiny vacuoles within this large vacuole and these granules as already mentioned may often be seen when the illumination is adequately adjusted.

When formalin-fixed sections are stained with Pasini's mixture or when Helly-osmic-fixed sections are stained for mitochondria, a series of different pictures immediately becomes apparent. At least in our cases, the optically empty vacuole is the exception rather than the rule. Instead, a mass of delicately stained particles (pale blue to dark blue with Pasini's stain and light green to emerald green with a modification of Altmann's stain) are now distributed in regions corresponding to the clear vacuoles seen in haematoxylin and eosin-stained sections (Fig. 11, a and b, and Fig. 14, a and b) More-

over, these special stains permit the recognition not only of several stages in the formation of the clear vacuole but also of the modifications in the related cytoplasm.

Vacuoles appear to form predominantly in mitochondria-rich cells or in cells in which there is an abundance of chromidial substance or microsomes and in which some stainable glycogen is to be found. In such cells the mitochondria may be filamentous, spherules, rodlets or, occasionally, large prismatic bodies extending completely across the cell such as we have described in some pellagrins (Gillman and Gillman, 1948). Vacuoles also develop in the very dark type of liver and which contains an abundance of mitochondria and usually also of glycogen.

In their simplest and earliest recognizable form the precursors of the vacuoles are represented by small clusters of minute green or blue-staining particles which have features indistinguishable from Claude's microsomes (1946a,b,c). Sometimes a larger fuchsinophilic particle may appear to be lodged in the centre of a tiny cluster which may be about 1 to 2 micra in diameter These clusters may merge with the cytoplasmic granules or they may remain discrete masses (Fig. 13,a). Some of the discrete clusters even at an early stage may be circumscribed by a fuchsinophilic rim apparently derived from a fusion of related mitochondria in the same way as often occurs around fat globules (Gillman and Gillman, 1948). Whether or not this fuchsinophilic membrane precludes the fusion of related clusters is not easy to decide, but it may be affirmed with some assurance that as the granules disappear, the fuchsinophilic rim becomes more emphasized and when the vacuolar contents are reduced to a minimum, only a large fuchsinophilic particle or rodlet persists for a time at least in a seemingly optically empty space (Figs. 9 and 10). This particle can be larger than any of the largest spherical mitochondria; at this stage this type of vacuole can be easily mistaken for a nucleus (Figs. 12, 13 and 14). On the other hand, small clusters of particles may not acquire a fuchsinophilic rim. These clusters continue to enlarge by an accession of particles emerging from the ground substance. Such clusters may fuse with neighboring ones to form bodies which may be as large as the nucleus (Fig. 17,a) or they may almost fill the greatly enlarged cell (Fig. 15). In the latter instance the granular contents are easily recognized.

Both the small and large bodies are usually located in the part of the cell where the mitchondria are most abundant. Although the spherical bodies form in mitochondria-rich cells, the continued growth of these bodies is associated with a sharp reduction in the number of mitochondria. The bodies, however, are usually lodged in the part of the cytoplasm where mitochondria are most abundant. When such large bodies or clusters develop a fuchsinophilic rim they, too, may often be mistaken for the nucleus, especially when one of the tiny small particles may become progressively separated by a water-clear ground substance (Fig. 13,b and Fig. 15). At the same time these particles may lose their affinity for stains so that a round or oval area is formed in which a round or rod-like inclusion may be lodged (Figs. 9 and 10). In such cases the translucent particles are recognized with difficulty. This now results in one type of vacuole.

On the other hand, once the spherical bodies are formed, instead of becoming translucent, the constituent particles of these bodies acquire a greater affinity for dyes (Fig. 11,a): they fuse and in this way form a small mass of homogeneous colloid and this assumes the same shape as the body from which it was originally derived. The cell may then contain several small masses of colloid (Fig. 11). In some cases, the colloid is thereafter rarefied and the staining properties are gradually lost. Various stages in this process are seen in Fig. 11. All the colloid may then disappear completely and a large irregular clear area persists in the cell. When several large masses of colloid disappear in this fashion, the cells acquire a morphology, chracteristic of the plant-like cell to be described later (Fig 7). Sometimes the rarefaction occurs within the centre of the globule of colloid. The centrally situated clear area thus produced may increase at the expense of the peripherally related colloid until eventually an optically empty vacuole may be surrounded by a narrow incomplete rim of colloid (Fig. 11,c). This rim probably corresponds to the flimsy strands of eosinophilic material noted in haematoxylin and eosin preparations and described originally by Rotter and Mueller. In such vacuoles, the translucent granules of the bodies are no longer discernible. This is at once evident from a comparison of sections stained in the same way and portrayed in Fig. 15. The minute particles in some obscure way have undergone a change from a more solid to a liquid phase.

As already mentioned, the spherical inclusion may already have appeared even before the clusters of micro-

FIG. 9. Cells showing vacuoles containing spherical inclusions. Note cell in centre of field contains an inclusion body lying in contact with flattened portion of the nucleus. This cell resembles a spermatid with its acrosomal vesicle and acrosomal granule. X 875, stained with iron hæmatoxylin. From a case of carbon monoxide poisoning.

FIG. 10 Another portion of the same liver as in Fig. 9 to show numerous vacuoles, each containing an inclusion body. Note also different sizes of inclusion body. X 875, stained with iron hæmatoxylin.

FIG. 11. A cluster of cells containing large vacuoles. These cells are now almost plant-like cells. At "a", the discrete granular contents of the vacuole may be recognized; at "b", the granules are fusing to form colloidal material. In the centre of the field "c", an optically empty vacuole may be seen containing a few thread-like inclusions, the other vacuoles in the same cell either contain colloid or granular material in the process of being converted into colloid. X 1,000, stained with Pasini's mixture. A case of fatal hæmorrhage following a stab into a pulmonary artery.

FIG. 12. Numerous large granular vacuoles surrounded by a definite membrane. Note the prominent spherical inclusion body at "a" and also the uniform size of the granular contents. X 1,000, strained with Pasini's mixture. From a case of prussic acid poisoning.

somes are sufficiently discrete to be regarded as constituting a distinct body. Thereafter the particles aggregate around the prospective inclusion and they increase in size, acquiring an intense affinity for stains. In Fig. 17,a, a photomicrograph of a section stained with a modification of Pasini's mixture, the minute particles constituting the several bodies shown at *a* are stained such an intensely blue colour that it is only just possible to recognize the fuchsinophilic spherical inclusions. On the other hand, the inclusion sphericle may appear later when the discrete particles are more clearly visible. In both instances, however, the inclusion may persist until the bodies have enlarged considerably, assuming the size in some instances equal in diameter to one or even three times the size of the nucleus (Fig. 12 and 14).

When several vacuoles appear in the same cell, some may contain the spherical inclusion, while it may be absent from others (Fig. 9, 10 and 12). The size of these inclusions may vary considerably and does not appear to have any relation to the size of the vacuoles (Figs. 10 and 14). The inclusion may be first visible in well-stained iron-haematoxylin preparations or they may be so large that they almost half-fill the vacuole (Fig. 10. It has been our experience that inclusions are much more frequently found in the livers of still-born infants than in adults.

The inclusions are most frequently single but occasionally they may be double. In the latter case, they may be widely separated or they may be in such close apposition that they result in a dumb-bell shaped inclusion.

The rodlets and thread-like inclusion described by Pappenheimer and Hawthorne and which we have occasionally seen in our series of livers, have a different origin from the spherical inclusion. They appear to be derived from the membranes separating contiguous vacuoles which have fused to form a large vacuole. In the cell containing the large vacuole filled with granular contents (Fig. 15), two smaller vacuoles can be seen near the twin nuclei. In the one, part of the wall of a vacuole has disappeared, while in the other it is still complete. The prominence of these walls is related to the fuchsinophilic properties as depicted in Fig. 14, b, which is a feature of some of the vacuoles as described above. In Fig. 13,b, a part of the fuchsinophilic membrane is still in contact with the periphery, while in the related vacuole a large rod-like fuchsinophilic inclusion is lying free although a delicate thread may be seen stretching from the rod to the periphery of the vacuole. This rod, together with the thread, is the remains of the wall separating two vacuoles which have now run together. Frequently, these fuchsinophilic walls may persist as delicate threads lying free within the vacuole. In such cases they may form rather complicated patterns.

We have gained the impression that vacuolar structures usually develop in cells containing an abundance of chromidial substance. As the vacuoles increase in number and size there is also a reduction in the amount of stainable chromidial substance. We are also satisfied that the precursors of the vacuoles arise in glycogen-rich cells and that the glycogen becomes sharply reduced when the vacuoles enlarge and become more numerous. Whether the glycogen, mitochondria and chromidial substances participate directly in the formation of the vacuoles is difficult to decide. At any rate, it can be claimed that the type of metabolism which is conducive to vacuole-formation is associated with a reduction in stainable mitochondria, chromidia and glycogen. There is more than sufficient evidence from our investigations that iron-containing cells in cytosiderosis do not easily develop vacuoles, but once such vacuoles appear stainable iron at first becomes arranged around such vacuoles and then later is sharply reduced in the cell. Often in livers the plant-like and vacuolated cells can be easily detected under low power in appropriately stained sections by the absence or sharp reduction in the iron pigment (Fig. 22). It would thus appear that even in advanced cytosiderosis of the gravity portrayed in Fig. 22, the iron pigment can be mobilized rapidly if the appropriate metabolism is produced.

The nucleus in the early stages does not exhibit any change which can be consistently correlated with the formation of vacuoles. The nucleus exhibits a wide range of morphologies even in non-vacuolated cells. However, when the cell is filled with vacuoles the nucleus is often very hyperchromatic. It should be noted here that sometimes large chromatolytic nuclei may be associated with cytoplasmic vacuoles, as in plant-like cells (Fig. 6). Such nuclei are not a specific feature of livers in anoxia, for we have frequently detected their presence in the fragments of liver removed from living infant and adult pellagrins by aspiration biopsy. We have consistently found them in biopsy fragments removed from young and old diabetics.

Congestion of the sinusoids was a variable feature i livers of patients dying from anoxia even in the livers of still-born infants. While vacuoles are frequently seen in congested areas of the liver, we were unable to establish any correlation between vacuolation and the degree of congestion in adults as did Trowell in

FIG. 13. Liver cells showing spherical inclusion body in large clear vacuole of "a", rod-like inclusion body at "b" and inclusion bodies surrounded by very granular material at "c". X 1,000. A case of carbon monoxide poisoning.

FIG. 14. A granular vacuole without an inclusion body and without a thick limiting membrane as depicted at "a", and at "b" a very large vacuole containing granular contents and a spherical inclusion, lying in a binucleated cell. X 1,000, a Pasini's stain. A case of carbon monoxide poisoning.

FIG. 15. A very large vacuole, filled with granular material lying in a binucleated cell. Near the two nuclei the remains of the fuchsinophilic membranes of the vacuole may be seen. This vacuole has fused with the larger one. Immediately above the nucleus, a membrane still separates the contents of a smaller vacuole from that of the larger one. X 1,000, Pasini's stain. From a case of asphyxia (throttling).

FIG. 16. Note the granular nature of the thick rim around a large clear fat vacuole. In frozen sections, the clear vacuole stains with Sharlach and the rim stained in this figure remains an optically empty rim. X 1,000, Pasini's stain.

his experimental animals. However, in still-born infants we did find that vacuoles were very commonly found in intensely congested livers, although they were often also found in anaemic livers. In view of our experience in adults and infants, we hesitate to ascribe the vacuoles only to the transudation of fluid from the sinusoids into the cells.

While the recent work of Opie (1947) has demonstrated that exposure of the liver cells to hypotonic solutions results in a loss of stainability of the mitochondria and the formation consequently of foamy cytoplasm, the effects so achieved bear no relation to the phenomena noted during the various stages leading to the formation of vacuoles. Since vacuoles are not post-mortem artefacts, they become a manifestation of an altered metabolism. While congestion of the liver may facilitate such a metabolism, this is to be regarded as an incident in the development of anoxia and not necessarily related causally to the formaton of the vacuoles, which may appear in livers where there is little if any congestion. We cannot accept Trowell's view that fluid cannot accumulate in the "space" between the sinusoidal reticulum and the liver cell but instead passes directly into the liver cell. By various techniques we are able in baboons to produce large pools of fluid in this space. Besides, both Eppinfer (1938) and Rossle (1933) have reported fluid in this space and when excessive have named the reaction "serous hepatitis". This we have also seen in some cases dying from carbon monoxide poisoning, but it is the exception rather than the rule. While we do not deny that in anoxia the contents of the liver cells are transforming from a solid to a more fluid state, such a transformation is the consequence of modication in metabolism rather than a manifestation of simple osmotic phenomena whereby fluid is able to pass from the congested sinusoids to be segregated in the cytoplasm of the liver cell; if this were not the case it would not be possible to account for the complex transformations described in the cytoplasm, associated with the formation of the vacuole.

The vacuole therefore represents a manifestation of an altered metabolism which may be found in deaths immediately attributable to anoxia. It cannot be expected that the vacuole will always exhibit the same type of morphology. The round or oval, optically empty vacuole is merely one of the patterns adopted by the vacuole during its evolution. When isolated from preceding events in its morphogenesis it is reasonable to presume that such a vacuole represents a segregation of fluid which Trowell derived immediately from the blood plasma. The peculiar morphogenesis of the vacuole, its variable relation to the sinusoidal pole of the cell, the associated modifications in other cytoplasmic inclusions, would all strongly suggest that the events leading to the formation of the vacuole are the consequence of a peculiar metabolism emerging rapidly in the special conditions associated with anoxia. Whatever fluid does accumulate in the vacuole is the consequence of a local metabolic process rather than only an increased permeability of the sinusoidal wall and of the cell membrane.

The plant-like cell

The plant-like cell has a very distinctive morphology (Figs. 3 and 4). When fully developed, this type of cell is about 1½ times or more the size of the ordinary liver cell. In haematoxylin and eosin preparations, the accumulation of a narrow zone of basophilic material containing a number of eosinophilic rodlets or spherules in the periphery of the cell, emphasizes the cell wall which seems to acquire a double contour. If allowance is made for the curious arrangement of the cytoplasm, it is evident that the cell membrane is actually thin though very sharply defined. The nucleus is located near the centre of the cell and is embedded in an irregular mass of basophilic cytoplasm which is continued along three to five widely separated strands (Fig. 3). These strands become continuous with the basophilic rim in contact with the cell membrane. The several strands of cytoplasm sub-divide the cell into a number of rectangular or trapezoidal compartments which most probably contain some fluid but which usually appear to be devoid of any structure.

In Helly-osmic-fixed tissues stained by Dry's method the cell is seen to be devoid of mitochondria except around the nucleus, along the cytoplasmic strands and near the cell membrane (Fig. 8). In these special situations the mitochondria are in the form of long delicate filament or short coarse rodlets or even spherules, and usually associated with translucent globules. Both glycogen (Fig. 18) and chromidial substance are sharply reduced and these, too, are distributed in the same parts of the cell as are the mitochondria. While fat globules are sometimes found in the plant-like cell, they are usually absent from the clear areas within the compartments.

Again, as in the case of the vacuoles, the events leading to the formation of the plant-like cell were reconstructed by arranging in a serial order the types of cells which we believe to be significant in the genesis of this type of cell.

An increase in ground substance with a consequent dispersal of the closely packed mitochondria may be regarded as an early stage in the formation of the plant-like cell (Fig. 5). This is associated with a significant increase in the size of the cell. This type of cell, now containing much ground substance and dispersed mitochondria, may have little significance when taken out of its context which includes all the other intermediate stages in the genesis of the plant cell; it is similar in many respects to a cell containing much glycogen, as often seen in recovering fatty livers. However, when considered in terms of the other stages resulting in the plant-like cell and observable in the same liver, then the above-mentioned cell does not become significant as a precursor of the plant-like cell.

With the greater dispersal of the mitochondria, fine translucent particles come into view. At first widely dispersed, they are later segregated into clumps occupying the spaces between the mitochondria. These clusters of particles increase in size, fuse with neighbouring

clusters until they fill a large segment of the cell. Simultaneously, the mitochondria lose their affinity for dyes, and thereafter they seem to merge gradually with the ground substance from which eventually they cannot be differentiated. Frequently, the mitochondria assumes a spherical form and only then disappear from view. Only a few robust mitochondrial rodlets persist around the nucleus, and distributed also along the cytoplasmic strands and below the cell membrane. In mitochondrial preparations, the clusters of translucent particles occupying the spaces between the cytoplasmic strands may acquire a greenish tinge: later the dye becomes suffused throughout the rectangular compartment and the individual particles lose their discreteness as they merge to form a green-staining body which stains an orange colour when Pasini's mixture is used (Fig. 7). There may be several such bodies and these may be surrounded by mitochondria. Some of these bodies may fuse and the resulting mass thus formed occupies an area about the size of the nucleus (Fig. 7, a). With the enlargement of these masses, the staining affinity is gradually lost and eventually the masses become completely translucent, occupying a large optically empty area of the cell (Fig. 7, b).

It should be mentioned that the green-staining bodies are indistinguishable from the precursors of the vacuolated cell. In the plant-like cell, however, the green bodies may fuse to form large masses of colloidal material occupying an area of the cell equivalent to about three times that of the nucleus (Fig. 7,c). With the gradual loss of affinity for dyes, the colloid is gradually converted into optically empty material filling a large compartment within the cell. At one stage the space may be occupied in part by an optically homogeneous material and in part by colloidal matterial.

It may be gathered from the foregoing that the plant-like cell and the vacuolated cell develop in very much the same way. The former may be regarded as a much more advanced reaction than the latter. In both instances it may often happen that optically empty vacuoles or compartments in the cell may form without exhibiting the several peculiar morphologies mentioned above. This is especially the case in haemorrhage where the plant-like cell may appear rapidly in the liver without the cytoplasm developing any special affinity for dyes.

The plant-like cells usually occur in clusters (Fig. 2 and Fig. 5); they may be distributed throughout an entire segment of a lobule or even throughout the entire lobule, although they appear first near centre of the lobule, two or three layers of cells removed from central vein (Fig. 2). In this connection it should also be added that there is a widely prevalent view that the portal tracts are consistently separated by a rather constant distance from the hepatic vein radicles. This is not entirely in accordance with our observatons, as determned from numerous injected specimens and of serial reconstructions of human and animal livers. Large hepatic veins may cross the portal tracts and in fact may appear to be encased by the same layer of connective tissue. This is particularly significant as far as the distribution of the plant-like cells is concerned, for sometimes when they appear to be located around the portal tract (Fig. 3), examination of serial sections usually reveals the proximity of an hepatic vein radicle. This does not mean, of course, that some types of reactions do not show a predilection for the central region of the liver lobule as happens in the case of poisoning with chlorinated hydrocarbons, but care is always necessary in localizing a reaction, particularly when it is associated with a modification in the vascular pattern.

In some favourable specimens in our collection the plant-like cell reaction is very intense, and the position of the central veins may be beautifully outlined by the clear cells. In Fig. 2, a mass of the plant-like cells is seen extending between two central veins and a portal tract may just be seen crossing at right angles to this mass. However, sometimes the plant-like cells have a focal distribution, affecting some lobules and not others in the same way as have been described in the case of the vacuolated cells.

Wherever the plant-like cells are to be found, the related sinusoids are usually closed or narrowed (Fig. 3 and 4). This is not to be regarded as the consequence of the enlargement of the cells, such as has been usually presumed in the case of the fatty liver: it represents an expression of the metabolic disturbance in the liver no less than does the development of the plant-like cell itself.

Necrosis of liver.

One of the consequences of the plant-like cell and the vacuolated cell reactions is often necrosis. Bywaters (1947) has described midzonal and paracentral necrosis. In his series of cases, the earliest degenerative change was found 8.5 hours after release following a crush injury. In this instance the liver showed the presence of eosinophilic globules in the spaces between the liver cells and the sinusoids. There were also "small intracellular hydropic, non-fatty vacuoles somewhat similar to those described by Kritzler and other in anoxia conditions." The earliest indication of necrosis was noted in a case 24 hours after suffering a fractured pelvis complicated by gas gangrene. In this instance Bywaters again emphasized the presence of fat-free vacuolated cells.

For the sake of completeness we have included the livers of two individuals who survived 9¼ and 24 hours respectively after exposure to carbon monoxide, i.e., apparently 21¼ and 36 hours respectively after first application of the stimulus. In these instances the carbon monoxide did not reach the concentration required to produce rapid death. A fuller report will be given at a later date of a large series of cases surviving for a much longer period after suffering a severe haemorrhage, multiple injuries or who experienced severe anoxia as a result of other causes.

In the first case of carbon monoxide poisoning in our series there was intense congestion in the central zone where the shrunken liver cells contained numer-

ous large clear vacuoles. In the second case, the inner two-thirds of the lobule had undergone extensive degeneration (Fig. 19). The sinusoids were engorged with blood but only in the most extensively damaged area was the sinusoidal wall sufficiently disrupted to permit the scattering of red cells into the perisinusoidal space related to the degenerated cells. Near the central vein the liver cells were very reduced in size, assuming an oval or round shape; the cytoplasm was intensely eosinophilic, the nucleus small and very hyperchromatic; near the mid-zone, small clusters of eosinophilic debris containing the remains of a hyperchromatic nucleus signalled the last phase in the disintegration of the liver cells. Further outwards towards the portal tract but still within the area of degeneration, the liver cells were smaller than usual but they contained numerous large vacuoles. This type of necrotic reaction conforms in general to the one described and portrayed by Oertel (1927) in chloral hydrate poisoning. The hepatic cells are primarily affected and the vascular changes are secondary. Although large areas of liver may be involved, the reaction remains essentially one of cytolysis of the liver cells. Only later does the affected area become engorged with blood to produce the picture typical of haemorrhagic necrosis.

As far as we have been able to reconstruct the events leading to cytolysis, it would appear that within a very short time after exposure to carbon monoxide, the vacuolar pattern of reaction is evoked, followed rapidly by the development of plant-like cells confined mainly to the central zone of the lobule. After a variable period of time which may be as short as from 9½ to 24 hours but usually even longer, the cell loses its fluid, the cytoplasm and the cell membrane contract on to the nucleus eventually to form round masses of eosinophilic material enclosing a small homogeneously basophilic nucelus. The cells immediately beyond the area of degeneration may remain vacuolated and these may recover or they, too, may eventually degenerate to a greater or lesser extent. The reticulum related to the plant-like cells usually loses its affinity for the aniline blue, but with the return of the circulation may stain intensely once again. The rupture of the wall of the sinusoids is a secondary event.

The events leading to necrosis can be appreciated graphically from an examination of Fig. 5, Fig. 2, Fig. 3 (a high-power study of part of Fig. 2) and Fig. 19. It should be added, however, that necrosis is not necessarily the inevitable consequence of the plant-like cell type of reaction. There is adequate evidence from our material that death may supervene after severe anoxia without there being any morphological evidence of severe liver injury of this nature.

THE FAT-FREE AND THE FAT-CONTAINING VACUOLES OF THE LIVER CELL

While the contents of the fully-formed vacuoles described above do not exhibit any affinity for the usual fat stains, there are several features in their genesis which are reminiscent of cells forming or losing their fat droplets. Moreover, during their formation or absorption the large fat droplets frequently develop a moth-eaten appearance due to the formation of a variable number of fat-free vacuoles (Fig. 20). Sometimes a single clear vacuole may appear within the large fat globule and this vacuole may continue to enlarge until it is coated by a narrow rim of fat. On the other hand, a vacuole may form excentrically and by its growth, at the expense of the fat, the clear vacuole may replace the greater part of the fat which remains as a round droplet lying in a clear space (Fig. 21, a). In such instances, the picture presented in sections treated with modified Pasini's mixture is similar to that depicted in Fig. 16, where part of the rim of the vacuole stains a faint b' colour. It can be difficult on occasions to decide in paraffin-wax-embedded tissues whether such a clear vacuole as shown in Fig. 16 is not developed in relation to the disappearance of fat. Then, too, as we pointed out in the fatty livers of pellagrins, the fat droplets may be completely surrounded by a watery-clear rim of cytoplasm having a varying width (Gillman and Gillman, 1945).

In the type of cell where the cytoplasm is filled with fat, the mitochondria are numerous and the glycogen may even be abundant; but once the fat begins to absorb, the mitochondria are reduced and the glycogen may increase sharply. However, a number of granular, basophilic bodies appear in the cytoplasm similar to those described as the precursors of the vacuolated cell. Similarly, in cells rapidly accumulating fat, frequently small aggregations of minute particles, at first baso-

FIG. 17. Note at "a" the vacuoles containing intensely staining granular contents and that each vacuole contains a inclusion body. Two vacuoles are lying in one cell; with a single vacuole in an adjacent cell. X 1,000, Pasini's strain. A case of drowning.

FIG. 18. Plant-like cells stained for glycogen. Note the scanty glycogen in the majority of cells and the abundant glycogen in some of the peripherally situated cells. Same case as liver shown in Fig. 8. Alcohol fixed tissue. X 875. Best-carmine.

FIG. 19. Necrosis of the liver in a case of carbon monoxide poisoning dying 36 hours after exposure to fumes. Numerous chromatolytic nuclei are seen in cells around the portal tract. Some parts of the liver contained cells similar to these depicted in Fig. 2. X 50, stained with hæmatoxylin and eosin.

FIG. 20. Liver of infant pellagrin stained with Sharlach to show numerous clear vacuoles in fat globule. X 650.

FIG. 21. Liver of another infant pellagrin stained with Sharlach to show clear vacuoles surrounding fat globule. At "a" spherical fat globule surrounded by a clear vacuole. Compare with Fig. 16. Note that the clear vacuoles are not entirely optically empty; a clear film of material can be seen in each vacuole, and in two cells near the centre, the film has been wrinkled during preparation of the section. X 650.

FIG. 22. A severe type 3 early type 4 liver, to show the great reduction of iron in the plant-like cells while related liver cells in the portal tract are crowded with iron pigment. A case of fatal hæmorhage. X 325, stained for iron by Dry's method.

philic, represent the precursors of fat. This we have repeatedly confirmed in the livers of rats poisoned with one of the chlorinated hydrocarbons. Furthermore, in the genesis of the clear cells or ghost-like cells located around the central vein, the cytoplasmic contents behave in very much the same way as do those of the vacuolated or plant-like cell. The closely packed mitochondria are separated by an accumulation of a water-clear ground substance and the cell may more than double its size; the stainable glycogen disappears rapidly, the mitochondria progressively lose their affinity for fuchsin and may be converted into very delicate threads, just visible under the highest power of the microscope. Some of the mitochondria may persist as coarse spherules or rodlets; small clusters of minute particles become arranged in form of spherules which in the early stages are surrounded by coarse mitochondria. These spherules may remain discrete or they may fuse to form large round bodies which may later become osmiophilic, although some may lose their staining reactions and remain as optically empty spaces. Some of these bodies may stain a faint green with Dry's modified mitochondrial technique or blue-green with Pasini's mixture. Often in the same cell some spherical bodies are osmiophilic and others react with the methyl green, while still others again may react only slightly with osmic acid. In this way are formed the ghost-like cells, such a distinctive feature of livers of rats poisoned with chloroform. Neither the fat nor the vacuoles are directly derived from mitochondria, although the products formed from the disappearing mitochondria may participate in their formation.

A close relationship exists between the fat globules and the fat-free vacuoles of the liver cell; the appearance of both types of structures is preceded by a similar type of transformation in the cytoplasmic inclusions. The very fact that both structures may develop simultaneously in different cells of the same liver or even within the same cell, still further strengthens the relationship between these different kinds of vacuoles.

The vacuolar type of reaction is much more rapid than the fatty one. According to Trowell's observations in rats and our own in human cases of acute poisoning with carbon monoxide and prussic acid, fat-free vacuoles can appear within a few minutes. Fat droplets, on the other hand, develop only after 12 hours in rats poisoned with carbon tetrachloride. A similar sequence of events, therefore, results in the vacuolar reaction and in the appearance of fat. A subtle difference in metabolism permits the reaction to proceed in one or the other direction.

As will be indicated later in this study, the extensive vacuolation of the cell seen in the livers of chronically malnourished rats and in man, can occur in the absence of fat. We have strong presumptive evidence that such vacuolated, glycogen-free cells are extremely vulnerable and at the slightest provocation can quite easily pass into the next stage, with the emergence of extensive necrosis of the type depicted in Fig. 19.

From the foregoing it is quite clear that in searching for a greater understanding of the chain reaction culminating in the fatty liver, special consideration needs to be given to the metabolic process involved in the genesis of the fat-free vacuoles. The two problems are unquestionably closely linked together, although significant differences in respect of the behaviour of the mitochondria in fat-filled cell indicate the prevalence of a slightly different kind of metabolism as compared with the fat-free vacuolated type of liver cell. These two problems also have a direct bearing on the stages leading to necrosis of the liver or of any other organ.

THE INCIDENCE OF THE DIFFERENT PATTERNS OF REACTION IN VARIOUS TYPES OF ACUTE DEATHS

The incidence of two types of reactions (the vacuolated and the plant-like cell) in various types of acute deaths is shown in Table I. From this table it may be inferred that the vacuolation of the cytoplasm even of the milder grade is not an invariable concomitant of anoxia even when found after prussic acid and carbon

TABLE I

Incidence of vacuolated cells in the livers of subjects dying rapidly from various causes.

	Number of livers	Number showing reaction	showing no reaction	Type of Reaction: Plant-like: Diffuse	Plant-like: Focal	Vacuolated	Rarified cytoplasm	Chromatolytic nuclei
Suicidal Hanging	12	11	1	2	3	5	2	4
Judicial Hanging	87	78	9	15	26	11	26	1
Throttling	8	6	2	0	4	3	1	0
Prussic Acid Poisoning	5	4	1	0	1	4	3	0
Carbon Monoxide Poisoning	25*	25	0	0	11	13	5	4
Lightning	2	1	1	0	0	0	1	0
Drowning	7	5	2	0	1	3	2	1
Stab in large Artery	17	16	1	4	7	2	3	3
Stab in Heart	11	9	2	9	0	0	0	0
Multiple Injuries	40*	34	6	14	10	6	1	10
Fractured Skull	32	25	7	9	5	5	6	2
Ruptured Ectopic	4*	3	1	2	0	0	0	2
Still-born Infants	25	18	7	7	4	10	0	0
Total No. of Livers	275							

* 1 case each of necrosis of the liver except in carbon monoxide poisoning, where there were 2 cases.

anaemia, severe haemorrhage or states where the haemoglobin cannot carry oxygen efficiently as in carbon monoxide poisoning; secondly, to a lowered partial pressure of oxygen, or in extreme cases to the complete exclusion of oxygen from the respiratory system as in asphyxia; and, thirdly, to the inability of the tissues to utilize oxygen as in cyanide poisoning. If we are to establish a pattern of reactions for the liver in anoxia, it is essential to discover whether in all three categories of anoxia the liver does tend to exhibit a similar type of reaction. Once it can be shown that the liver tends to react in the same direction, irrespective of the cause of the anoxia, then perhaps some information may become available for the interpretation of the modus operandi of stimuli which produce similar reactions to those seen in anoxia but which superficially do not appear to be related to primary-anoxia producing stimuli.

The most consistent reaction in the liver occurs after a sudden haemorrhage. This is almost invariably associated with the rapid formation of plant-like cells, although the degree of the reaction is not always commensurate with the amount of blood lost. When no blood is lost from the body and the oxygen carrying power of the blood is seriously impaired as in carbon monoxide poisoning, plant-like cells may also be found in abundance but very frequently only vacuolated cells may be detected. Then, too, in asphyxia, as exemplified by drowning and throttling, vacuolated and/or plant-like cells are present in the liver. Poisoning of the cytochrome system so that cells lose their ability to utilize oxygen efficiently, as after the administration of prussic acid, also is associated with the appearance of vacuolated or plant-like cells. However, in the case of carbon monoxide poisoning, it can also be presumed that the cytochrome system of enzymes within the cell is seriously embarrassed. This perhaps may account for the frequency with which the reaction became arrested at the stage of vacuoles. It might well be that for the reaction to proceed from the vacuolar to the plant-like cell, the cytochrome system of enzymes is essential. This at first, might be suggested from the observations that in prussic acid poisoning the vacuolar reaction occurs more frequently than does the plant-like cell reaction, although both types of reaction can occur to a variable degree even in the same section of liver. Offset against this are the findings in throttling or drowning or even in judicial hanging, where, in the absence of immediate inhibition of the cytochrome enzymes by specific poisons, the vacuolated cells occurred almost as frequently as did the plant-like cells.

One conclusion may be drawn from this analysis, namely, that irrespective of the way the anoxia is produced, both plant-like cells and vacuolated cells tend to occur in the liver. Whenever plant-like cells or vacuolated cells are seen in the liver, it can be assumed (and is justified in terms of the above findings and analysis) that severe anoxia preceded death. This information now aids in the interpretation of the behaviour of the organism in respect of other types of injuries or diseases which are not known with any assurance to produce a condition of anoxia. Thus, in the case of severe head injuries or multiple injuries leading rapidly to death but not necessarily associated with much haemorrhage, both plant-like cells and vacuolated cells have been observed in a high percentage of cases in our series (Table 1). Since vacuoles are known to form before death (Trowell, 1946) it is not unreasonable to presume that the same occurs in human livers.

The similarity in appearance of the structure of the liver following different types of severe adverse stimuli, whether they be in the form of haemorrhage, injury to the body, fractured skulls and concussions, burns or some poisons, would seem to indicate that, irrespective of the mode of production, a state of anoxia rapidly supervenes and this may terminate fatally. Even where death does not result, these several types of stimuli are known to produce shock. It can be presumed with some justification that in these several conditions where a fatal issue is avoided, anoxia of greater or lesser severity also supervenes for a variable period at least before recovery. Whether the same extensive liver reaction occurs in a non-fatal shock produced in different ways still remains to be established by biopsies taken from the livers of shocked patients who eventually recover from the acute episode.

DISTRIBUTION OF THE VACUOLATED AND PLANT-LIKE CELL IN THE LIVER LOBULE IN DIFFERENT CONDITIONS

Although the various conditions listed in Table I generally result in the formation of vacuolated or plant-like cells, the liver is not implicated to the same extent. Only in haemorrhage and in still-born infants, as a rule, is the entire liver lobule often affected. In these conditions, too, sometimes, the reaction may be confined only to a part of the lobule. In such cases the most affected part is located near the central vein. However, we have also seen livers where only some lobules were affected and not others. Frequently, we have observed extensive reactions in some lobules and scarcely any change in closely related ones. Then, too, the liver may not always react in the identical way to the same lethal agent. In carbon monoxide poisoning, for example, vacuoles appeared in 13 of 25 cases.

It might then be asked why in the case of rapidly acting poisons like carbon monoxide and prussic acid, all parts of the liver do not respond uniformly. In the first place, death is immediately due to poisoning of the nervous system which in ordinary circumstances is alleged to be extremely sensitive to oxygen deprivation There is every likelihood in such cases that the poison has not been distributed equally throughout the entire liver. In the second place, not all parts of the liver are equally vulnerable to the same poison. This is shown in carbon tetrachloride poisoning where the lesions in the first instance are confined to part of the lobule near the central vein. Even then, the extent of the reaction is dependent on the state of the liver in respect of previous nutrition, as admirably demonstrated over 30 years ago by Opie and Alford (1914, 1915). Moreover, the liver lesion is also dependent on the amount of drug employed as well as on the time elapsing after its administration.

It is common knowledge that after the administration of large concentrations of chlorinated hydrocarbons

terms of function tests taken in conjunction with the metabolic performance of the liver cell.

The circulatory changes. Rein and Rossler (1929) demonstrated that eight minutes after removal of blood equivalent to 2 per cent of body weight, the blood pressure dropped by 20 per cent. The blood flow through the intestine diminished by 70 per cent, while there was an 82 per cent decrease in the flow through the femoral artery. Ten minutes after bleeding the blood pressure returned to within 5 per cent of the control value at which time the blood through the femoral artery rose 30 per cent while the flow through the intestine remained 20 per cent below its original value. This strongly suggested that the circulation through the intestinal vessels reacted quickly to the withdrawal of blood but did not recover as rapidly as did that of the peripheral vessels. Such a reaction in the intestinal vessels no doubt can can have particular repercussions on the circulation through the liver.

McMichael (1937) reported that after a severe haemorrhage a correlation could be established between the oxygen saturation of portal blood and the systolic blood pressure. He also demonstrated that when the oxygen saturation was low, much less oxygen was removed from the portal blood than was the case at higher levels of saturation. Even after a moderate haemorrhage in dogs the portal blood flow was reduced by 53 per cent (Blalock and Levy, 1937). It is also evident from the observations of Rein and Rossler, quoted above, that after haemorrhage even when the blood pressure has returned to within 5 per cent of its original value, the circulation through the intestine is still 20 per cent below its normal efficiency. From their analysis of pressure gradients during the period of haemorrhagic hypotension and shock, Wiggers et al (1945) concluded that the portal flow through the liver was reduced to a greater extent than was suggested by the changes in systemic and portal pressure, more especially because of the relative increase in portal over mesenteric resistance.

These several experiments after haemorrhage all lead to the same conclusion, namely, that portal circulation is implicated early and recovers tardily. They do not necessarily reflect the precise modification in the circulation through the liver. It can obviously make a great difference to the function of the liver whether the blood is short-circuited from the portal tract into the hepatic veins or whether it follows a devious course through the sinusoids. McMichael's observations relating to the inability of the portal blood at low oxygen saturation to lose less oxygen would seem to suggest that in this instance the blood is following a more direct course from the portal to the hepatic veins and that the sinusoidal pathway is not being effectively employed. This may still further embarrass the liver cells. Support for this view is provided by the investigations of Frank et al (1946), who demonstrated that if an adequate flow through the liver of a dog shocked by severe haemorrhage was maintained by continued transfusion from another dog, a high degree of protection was afforded against lethal consequences usually to be anticipated in dogs bled sufficiently to drop the blood pressure to 30 mm. With a blood pressure of 30 mm. following haemorrhage, 11 of 12 dogs survived after vivi-perfusion of the liver via the splenic vein, while 15 of 17 dogs treated the same way except that blood entered the jugular instead of the splenic vein, died after transfusion. In some of the liver-transfused dogs, the evidence of damage to the nervous system developed during the perfusion period, but this damage was transitory and disappeared after transfusion, except in isolated instances. This vivi-perfusion of the liver therefore seemed to provide protection against irreversible shock following haemorrhage. Frank et al were led to suggest that the sustained liver function bears some relation to the integrity of the peripheral vascular mechanism. This conclusion is in accord with previous observations.

It is now obvious that a sudden loss of a large amount of blood from any part of the body does have an immediate and even a prolonged effect on the portal circulation, and that the peripheral blood pressure may not necessarily reflect the extent of depression of the portal circulation.

Function tests and cellular metabolism in anoxia.

Influenced, no doubt, by the French investigators who noted toxic changes in the liver following shock, Aub (1920) was led to ascribe the consequences of shock to impaired liver function. The recent work of Frank et al (quoted above) is entirely in favour of this view point. Ireneus and Pueston (1944) conducted a number of liver function tests on dogs subjected to massive bleeding. In eight of 11 animals the galactose tolerance revealed an excretion of galactose in amounts far in excess of control dogs. The prothrombin time was prolonged in four of 11, while sulfobromophthalein sodium excretion test and the amount of serum phosphatase remained unaffected.

Indirect evidence of impaired liver function is suggested by the rise in amino acid concentration of plasma (Engel et al, 1943) and in blood lactate and pyruvate (Engel et al, 1943; Russel et al, 1943). Engel et al (1944) established a high degree of negative correlation between the blood amino nitrogen and the oxygen saturation of the portal venous blood. These several observations have been confirmed by in vitro observations of the behaviour of liver slices removed from shocked rats. Haist and Hamilton (1944) noted a fall in liver glycogen and decreased ability to synthesize glycogen from glucose; the oxygen consumption of liver slices is reduced, the liver loses its efficiency to de-aminate amino acids and to synthesize urea from *d-l* alanine and ammonium lactate (Russel et al, 1944).

Significant changes were found in the movement of liver potassium and sodium following bleeding sufficient to produce fatal shock (Darrow and Engel, 1945). There was a 10-25 per cent loss of liver potassium and an appreciable increase in liver sodium chloride. With prolonged repeated small haemorrhages, Darrow and Engel noted an even greater increase in liver potassium and a greater loss of sodium. The latter type of reaction is accompanied by an increase in liver water. The observations of Darrow and Engel are enormously enhanced by the fact that they were made from the same animals as those by Russel et al (1944), Engel et al (1944 and Wilhelmi et al (1946) for their studies on

rate of peripheral protein breakdown ensues from the anoxia and the amino acids and other products resulting therefrom begin to accumulate in the blood, since they are either not taken up or are not deaminated sufficiently rapidly by the liver. If the hepatic anoxia persists long enough actual damage to the liver probably occurs and this organ then begins to lose its ability to deal even with those amino acids which pass through it.

Greig (1944) discovered that anoxic tissues show a decreased ability to metabolize lactic and amino acids. This decreased oxidative ability is alleged not to be due entirely to co-enzyme distribution nor to an anaerobic accumulation of intermediate metabolites which inhibit oxidation but to the presence of a heat-stable non-dialysable enzyme-like substance in the tissue, and this substance inhibits the oxidation of lactic acid and amino acids. This enzyme-like substance appears to attack the apoenzyme or protein part of the oxidative system.

Burdette and Wilhelmi (1946) reported that the oxygen uptake of heart muscle slices from rats in the terminal stages of prolonged severe haemorrhagic shock is significantly less than normal, in the absence of substrates. When pyruvate was added the oxygen uptake was increased but still less than normal. Le Page (1946) examined the carbohydrate energy reservoirs and high-energy phosphate compounds in rats shocked by the Noble-Collip tumble method, and following the application and subsequent release of a tourniquet. The general manifestation of tissues in shocked animals were represented by elevated lactic acid and inorganic phosphate, low glycogen, adenosine triphosphate depletion, some phosphocreatine depletion and an abnormal accumulation of phosphopyruvic acid. The intermediary metabolites were also high for shocked animals. According to Le Page, the animals appear to expire because of exhaustion in the respiratory and vasomotor centres, though this is evidently preceded in certain cases by liver failure and probably by failure of the mechanisms for mobilisation of glucose from body protein, which conversion is necessary because the tissues must operate largely with anaerobic glycolytic mechanism. An earlier study by McShan et al (1945) also led to the conclusion that the modification in the concentration of metabolites in the blood was indicative of catabolic changes in the tissues, during the depletion of energy substances of which adenosine triphosphate was particularly important.

Sufficient evidence has been adduced to show that the extra-hepatic tissues, endocrines, striated muscle, heart muscle and brain are very extensively affected by a rapidly developing anoxia. While injury to the liver may have serious consequences for the organism as a whole injury to other organs and tissues in turn can be equally disastrous for the liver. The activities of the liver are regulated by the prevailing metabolism and the liver participates in a particular way in maintaining a particular steady state or homeostosis within the organism. The general attributes of the shock-state, therefore, are dependent on the emergence of a particular type of functional relationship between the several glands and tissues comprising the organism. Gross impairment in the function of any one of these tissues may eventually prevent the re-establishment of the type of metabolism which facilitates recovery from shock. If the liver is grossly injured then re-adjustment is greatly hampered or even made impossible, but failure of the adrenal may have equally devastating consequences.

It may be significant that the vacuolated and plant-like cells may be produced by a variety of different stimuli, such as insulin (Tannenberg, 1939), large amounts of adrenalin (Davis, 1939), high-altitude anoxia (Mueller and Rotter, 1942; Trowell, 1946; Kritzler, 1942), carbon monoxide (Trowell, 1946; Kritzler, 1946), and which we have also confirmed in man and rats, haemorrhage, multiple injuries, burns, drowning, asphyxia of new-born infants, head injuries (present authors), crush injury (Bywaters, 1946). In short, this reaction may be evoked by the common conditions which are known to produce shock.

The vacuolated cells appear extremely rapidly and therefore may be regarded as one of the earliest indications of tissue injury. Furthermore, it is evident that the pathway whereby this reaction is evoked is apparently not always identical. The sequence of events following the administration of insulin is obviously not the same as that observed in severe haemorrhage or after injection of large quantities of adrenalin, although the end result is very similar. However, once shock has been induced, then the changes in the tissue appear with great rapidity. It is unlikely that these gross reactions are not preceded by significant alterations in metabolism, although at first these may not be sufficiently gross to be detected immediately, but they become manifest sooner or later with increasing intensity. These reactions are associated with an accumulation of abnormal or excessive amounts of particular metabolites. Catabolic changes are rapidly initiated; the basal metabolism drops, the venous oxygen tension announces the changes from an aerobic to a more anaerobic type of metabolism, the temperature drops and the circulation is sharply depressed. In this process several organs like the liver, the brain, the adrenal and heart may suffer severe organic injury. As will be shown in a later communication, the abnormal products of this type of anaerobic metabolism may then initiate a new set of reactions. One of the consequences of this anoxia as revealed by Bywaters and which we can amply confirm, is extensive necrosis of the liver. Similar extensive injuries, however, may be inflicted on the brain, repeatedly described in the case of carbon monoxide poisoning and as has been shown in our laboratory in the case of carbon tetrachloride poisoning (Huntley, unpublished data).

The effect of the acute phase of anoxia depends largely on the state of the organism at the time of the acute episode, upon the severity of the stimulus and upon the way the stimulus has provoked the anoxic state. We have shown that severe haemorrhage especially from an abdominal organ affects the liver violently and with great suddenness. In such instances, the reactions leading to shock may not follow in the sequence which occurs in the case of insulin or adrenalin shock. This leads us to assert that shock is a pattern of reactions which is the consequence of a vast array of different stimuli which have a common end result, namely, the

production of a state of acute anoxia. This state may be induced by specific agents such as carbon monoxide or prussic acid, by interference with the oxygen transportation mechanism, by injury of the tissues with the liberation of metabolites as after burns or crush injury, irradiation with ultraviolet or X-rays, by irritation of the nervous system. The efficiency of each of these stimuli in the production of shock and of the vulnerability of any organ depends a great deal on the way the organism is poised at the time of application of the stimulus. The exposure of rats to a particular level of oxygen tension may not be adequate to produce liver injury, but if such rats are first thyroxinized, this same level of lowered oxygen tension may then precipitate necrosis of the liver (Melver and Winter, 1942). Similarly, mention has been made of the great increase in the amount of prussic acid required to kill rats with fatty livers. Then, again, insulin results in convulsions or coma. Such animals may be resuscitated by an electric shock without a corresponding elevation in the level of the blood sugar (Gellhorn and Kessler, 1943); the insulin convulsions may also be prevented by previous administrations of thyroxin (Komissarenko, 1943). It cannot always be anticipated, therefore, that the same intense stimulus will always result in the same degree of shock, nor that shock will always lead to the same type of injury and that all organs will be affected to the same extent. Actually, the investigations of Le Page have demonstrated that rats can be conditioned against stimuli which originally were capable of inducing a shock type of metabolism, and it can now be added that a modification in metabolism can alter the shock-producing effects of insulin or the lethal effects of prussic acid. The supervention of shock, therefore, is as much a reflection of the state of the organism as it is of the intensity of the exciting stimulus.

From what has been said above, no useful purpose can now be served in continuing the search for specific shock producing stimuli. Once it is accepted that several different and unrelated stimuli can produce shock, it seems more profitable now to elucidate the several different stages in the process whereby all the diverse stimuli mentioned above eventually lead to anoxia characteristic of shock. This may facilitate the elaboration of appropriate physiological techniques for arresting the shock-producing metabolism instead of persisting with the present methods of treating all stages of shock in all individuals in more or less the same way.

NUTRITION AND ANOXIA

Several reports in the literature have indicated that vacuolated cells are to be found in the livers of animals fed particular types of diets. With the aid of high carbohydrates, low-protein and also low-fat diets, Elman and Heifitz (1941) and Elman et al (143) have produced a reaction of the dog and rat in the liver cells which is indistinguishable from the plant-like cell described above in the livers of subjects dying from anoxia. In these plant-like cells stainable glycogen is either reduced or absent. Similarly, Ashburn et al (1943) have also reported vacuoles in cells of the liver and of striated muscle or in both following the prolonged feeding of purified diets to which sulphaguanidine had been added. These reactions were often associated with necrosis and arterial degeneration in many parts of the body, including the heart. In liver fragments removed by biopsy from adult pellagrins subsisting on a pure maize diet we have repeatedly noted plant-like cells indistinguishable from those described and depicted by Elman et al (1943) in dogs on a low-protein diet.

It is known that in pellagra and other forms of chronic malnutrition, metabolism is often depressed, that there is a profound disturbance in carbohydrate metabolism, that injury to the internal organs may be very profound (Gillman and Gillman, 1948). It seems more than a possibility that impairment of nutrition whether by the feeding of the types of diets used by Elman and his co-workers in the case of rats and dogs, or of the sulphaguanidine-containing diets of Ashburn et al, or of the type of diet consumed by Africans, may all result in a type of metabolism having features characteristic of chronic anoxia. We have strong reasons for believing that such chronic anoxia may not only impair the integrity of many organs and tissues, including the liver, the brain and the cardiovascular system, but indeed may facilitate the formation of products derived from different tissues, and these products may intensify the adverse effects of diet by the flooding of the circulation with macromolecules, which in turn may intensify the anoxic state, leading eventually to widespread and advanced organic diseases, including arterial degeneration.

It is again significant that some of the low-protein diets used experimentally may result in very fatty livers, while others lead to the appearance of plant-like cells. It is our experience that fatty livers are less susceptible to stimuli exciting acute necrosis than are livers containing many plant-like cells. While it would appear that the vacuolated cell may precede the formation of fat, it is evident that the type of metabolism permitting the emergence of the fatty livers requires conditions different in some respects from those permitting the development of vacuolated cells and plant-like cells. As already mentioned, plant-like, glycogen-free cells are often seen in adult and infant livers recovering from an attack of pellagra. Such cells belong to the category of plant-like cells. These may be regarded as strong presumptive evidence of the persistence of a state of chronic anoxia. Many infant pellagrins after making apparently excellent recoveries from the acute episode and after losing the massive quantities of fat from the liver, may die suddenly when least expected. At postmortem no gross pathology can be established to account for the catastrophe (Gillman and Gillman, 1948). In such cases it is not entirely unlikely that the persistence of a state of chronic anoxia coupled with some sudden exertion eventually results in one type of sudden death.

At any rate, it is clear that the vacuolated and plant-like cells are worthy of much greater attention than has been the case hitherto, more especially because they represent one of the end results of malnutrition, poisons and of many of the known shock-producing stimuli.

It is quite clear that an understanding of the factors

responsible for the appearance of these cells is not to be obtained only by an examination of physical phenomena such as the presence or absence of congestion, as suggested by Trowell, but rather by a meticulous analysis of the complex metabolic processes of the type employed in attacking the problem of the genesis of the fatty liver.

In conclusion, it should be added that it is a common practice to bleed animals as a preliminary to a correlative study of the cytology and the histo-chemistry of the liver cell of the type conducted by Claude (1944a) and others. A rapidly fatal haemorrhage in many circumstances can lead to a profound change in the nature and distribution of the cytoplasmic inclusions of the liver cell affecting at least the mitochondria, chromidia, glycogen and ground substance. When such a procedure is followed by perfusion with saline or other "physiological" fluids further disturbance in the morphology is to be anticipated. The interpretations of results derived from tissues obtained by such techniques is to be accepted with some reserve, more especially as some of the figures illustrating Claude and Fullam's (1946a) microchemical studies of the liver cell are very similar to those observed in our cases of acute anoxic deaths.

The rapid effect of anoxia on the liver seriously complicates all cytological investigations, for it is now difficult to know how best to kill an animal rapidly without affecting profoundly the structure of the liver cell. This technical difficulty requires careful consideration by those embarking on investigations where subtle modifications in the appearance of minute intracellular particles may significantly affect the interpretation of chemical data obtained from the same tissue.

SUMMARY

An examination of 275 livers of human subjects dying rapidly from asphyxia, haemorrhage, carbon monoxide and prussic acid poisoning revealed a high incidence of fat-free, glycogen-free vacuoles in the cells of the liver.

A distinction was made between cells having discrete, multiple vacuoles (vacuolated cells) and those containing few but larger rectangular or trapezoidal-shaped vacuoles (plant-like cells).

The pathogenesis of these two types of vacuoles was reconstructed in fixed and stained preparations. Inclusion bodies were seen in vacuolated cell but rarely in the plant-like cell.

When present, both types of vacuolated cells usually occurred in clusters which showed a predilection for the central part of the lobule, although on occasion these clusters seemed to be scattered in a haphazard fashion throughout the liver.

The incidence of these vacuolated cells was determined in different varieties of asphyxial deaths, in haemorrhage, in still-born infants and in acute deaths following multiple injuries but not necessarily associated with much haemorrhage. It was demonstrated that these reactions varied in intensity in different individuals dying from the same cause. An attempt was made to assess some of the factors which could alter the reactivity of the liver to the same kind of intense stimulus.

Since anoxia results in a high incidence of vacuoles in the liver cells and since all the conditions which caused anoxia can also lead to shock, it was concluded that in acute shock, anoxia rapidly supervened which could account for the metabolic disorders described in that condition.

This histological evidence disclosed that the liver was more rapidly and more diffusely affected by severe haemorrhage than by other stimuli, and this confirmed previous observations made by investigators using physiological and biochemical techniques.

While the liver was undoubtedly affected early in anoxia and perhaps could account for many of the reactions seen in acute and post-shock phases it was indicated that in anoxia the metabolism of other equally important organs could also be profoundly altered.

The relation of the vacuoles to fat was briefly examined and in the course of this analysis it was reaffirmed that many different kinds of fat-free vacuoles seen in a variety of conditions were related phenomena.

Attention was drawn to the close resemblance of the plant-like cell found in anoxia and the enlarged fat-free glycogen-free cells encountered in the livers of pellagrins and of protein-deficient rats and dogs. It was suggested that in some forms of chronic malnutrition a state of chronic anoxia supervened and this amongst other effects could stimulate the formation of water-clear cells in the liver.

It was demonstrated that the plant-like cell reaction could sometimes be followed by necrosis of the liver and this could be the genesis of acute necrosis described in nutritional experiments.

Finally, it was indicated that the results obtained by cytochemical and cytological analysis of liver tissue, might be influenced by the several techniques used for bleeding the liver as preliminary to such investigations.

We wish to acknowledge our indebtedness, firstly, to Professor R. A. Dart for his deep interest and substained encouragement; secondly, to Professor R. H. Mackintosh, of the Medico-Legal Laboratories, Johannesburg, for his helpful advice and for his courtesy and generosity in permitting us to collect much of the material used in this investigation; to Mr. Sidney Dry, who was responsible for the excellent slides which greatly facilitated our studies, we extend our grateful thanks.

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Sterilization of the Human Gut with Phthalylsulfacetimide

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Studies in the laboratory show that phthalylsulfacetimide is actively bactericidal against organisms normally found in the human intestinal tract. This property suggests an important usefulness of the compound in preoperative preparation for intestinal surgery.

To evaluate the drug for this purpose the bacterial counts of the stools of four normal adults were determined daily before, during and after the oral administration of 0.2 Gm. phthalylsulfacetimide per Kg. of body weight.

METHOD

A portion of the first stool of the day was collected directly into a dry, sterile Petri dish, which was then covered and kept refrigerated at 4°C. until ready for use. Then the entire specimen was emulsified in sterile physiological saline and filtered through sterile gauze into a graduated centrifuge tube described below, which was then plugged with a cotton and gauze plug secured by a rubber band. The emulsion was centrifuged for exactly 15 minutes at exactly 1700 revolutions per minute, using a tapered, graduated 15 cc. tube of 11.5 cm. length and 1.6 cm. inside diameter, the rim of which was 14.6 cm. from the axis of rotation at full speed. The supernatant fluid was discarded, and 1 Gm. of the sediment re-emulsified with 10 times its volume of sterile saline. Serial dilutions of the new emulsion were made using sterile saline, and exactly 1 cc. of each dilution was introduced into a Petri dish and agar pour plates made. The procedure was duplicated for lactose-fermenting organisms, using eosin-methylene blue agar. The agar must not be hot, but just sufficiently fluid to pour well. The plates were incubated overnight at 37°C. and colony counts made. In our experience plates containing more than 200 colonies were difficult to count with absolute accuracy. We therefore chose the serial dilution plate where the count was unmistakably clear. The count was multiplied by the dilution factor to determine the number of living organisms per gram of wet feces.

This procedure, showing the number of living organisms, obviously produces lower counts than a method which counts dead bacteria.

No effort was made in this study to identify the multitudinous species of bacteria normally inhabiting the human intestinal tract except that the lactose-fermenting or coliform organisms were cultured separately on standard differential media for the purpose of obtaining a separate count on this class of organism. Hence "total count" is necessarily qualified to mean that determined by aerobic procedure edscribed.

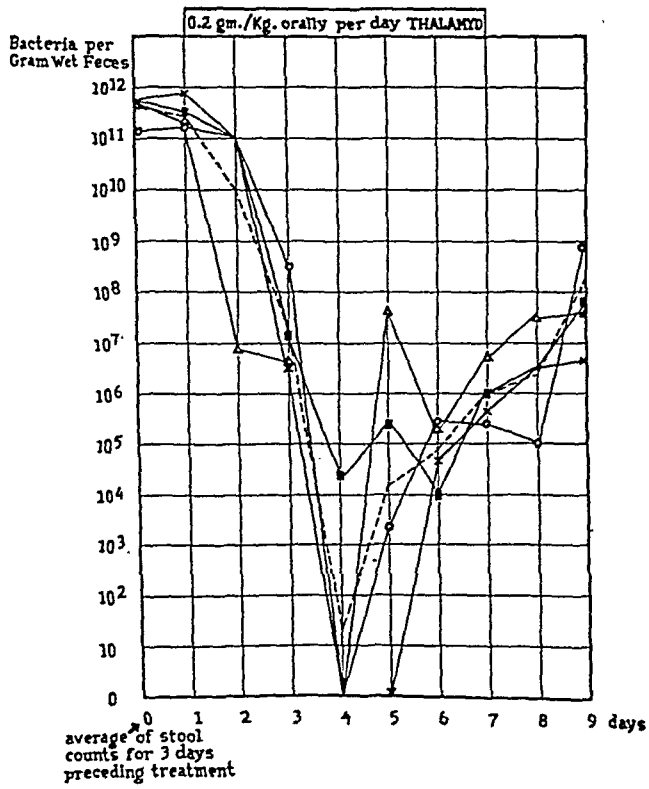
Certain errors characteristic of all procedures for counting stool bacteria are minimized by the precaution stated, such as uniform treatment in the centrifuge, refrigeration of the specimen until serial dilutions can be made in order to prevent the organisms from multiplying beforehand, careful watch over the agar temperature, etc.

A base line average of bacterial flora was determined from three successive daily stool counts before treatment with the drug was started. These counts ranged from 10^{10} to 10^{12} (average 7×10^{11}) total bacteria per gram of wet stool. Half this number were lactose-fermenting bacteria such as Escherichia coli. Beginning with the first daily count during treatment, there was evident a logarithmic fall in the number of organisms until, by the fourth or fifth day, three subjects showed a completely sterile stool while the fourth had a count of 10,000 total organisms (with 0 coliform bacteria) on the seventh day. The detailed findings in the individual subjects and the mean values appear on the accompanying graphs.

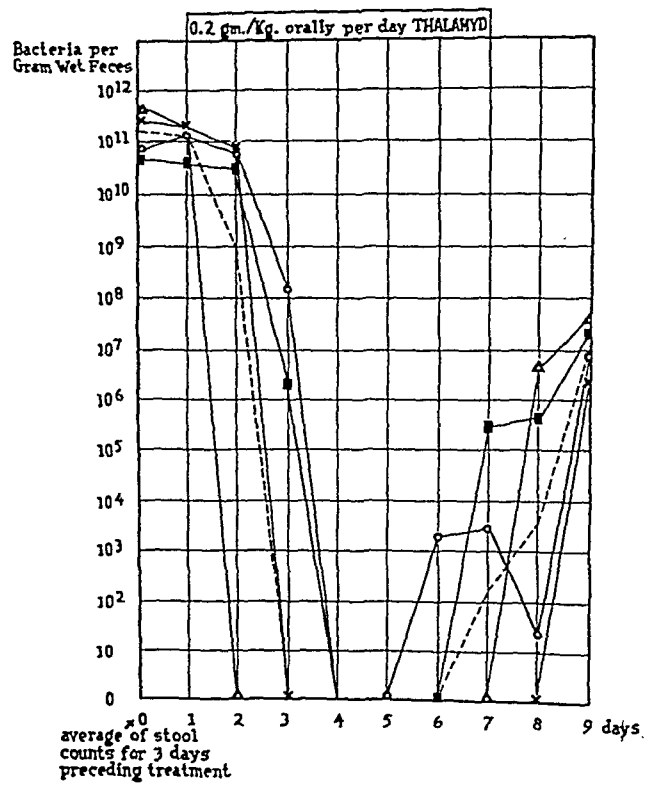
No evidence of toxic reactions of any kind attributable to the drug was observed in any subject.

The striking effectiveness of phthalylsulfacetimide in reducing the intestinal flora indicates its potential value in routine prophylactic preparation of the gut for intestinal surgery. The vitality of the operated tissue is a matter of the most fundamental concern, and the influence of infection, when present, is bound up inseparably with it, in terms of both cause and effect. Hence the desirability of an efficient, non-toxic mode of sterilizing the gut is self-evident.

All Organisms



Coliform Organisms



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NUTRITION

The Dietary Management of Chronic Amebiasis

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Amebiasis in North America and in the Caribbean usually follows the forms described by Craig as types I, II, or III. The symptomatologic characteristics of these types are very different from the classic, textbook picture of amebiasis with acute diarrhea, bloody stools, and other signs usually described in the manuals of internal medicine. Types I to III of Craig are characterized by chronic constipation, with occasional bouts of diarrhea or intermittent diarrhea and constipation. Prominent among the subjective symptoms are gaseous distention accompanied by pain or feeling of pressure along the colon, especially the cecal, hepatic, splenic, and sigmoidal flexures. Nervous symptoms may comprise the chief complaint, mainly if, as a result of long standing disease, spastic or mucous colitis has developed. Sigmoidoscopic findings in these types may vary from large typical amebic ulcers to normal mucosa, but more commonly will include small petechial "flea-bite" hemorrhages, in the rectum or sigmoid, with or without a hyperemic, thickened, edematous mucosa and valves coated with a glary cast. Edema of the mucosa with rectal valve "roughening" and nodularity is even more characteristic.

The X-ray findings in barium studies of the gastrointestinal tract with mucosal pattern visualization are variable.

The most frequent changes are formation of a "cecum pole," conization, contraction, and inversion of the cecum; cecal irritability, and edema of the mucosa. (Arendt[2]). The motility of the small bowel is often disturbed and the mucosal pattern may show loss of the feathery appearance of the jejunum.

A moderate normochromic normocytic anemia is present as a rule. The stools contain much undigested food and fat. Mucous is very often found during the bouts of diarrhea; blood, pus and macrophages may also occur. Charcot-Leyden crystals are very frequent. Red blood cells are only exceptionally ingested by the amebas. Due to the protean nature of the disease, there is a great variation in the stool findings even if daily fecal specimens are examined.

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Emetine is both ineffective and contraindicated in these types of amebiasis[1]. Oral arsenicals and iodine preparations commercially available at present do not always prevent relapses. Due to the very prolonged, chronic character of these types of amebiasis, discomfort often persists even after vigorous anti-amebic medication. Sequelae such as "irritable colon," "mucous colitis," are not alleviated by specific anti-amebic therapy, whether or no amebas are passed with the stools.

Because of these difficulties in the management of amebiasis, further therapeutic measures are strongly indicated. The most important of them is an adequate diet, providing sufficient calories, vitamins, and essential amino acids, without irritation to the bowel and without tending to produce either diarrhea or constipation.

The vitamin balance of persons suffering from amebiasis is often disturbed. The production and absorption of vitamin K and "B complex" is frequently diminished due to the altered microbial flora of the intestines. The inflammatory process requires a higher vitamin C intake.

With the exception of patients developing a sprue-like syndrome, the inorganic balance is not basically changed. The anemia which is frequently mistaken for iron deficiency anemia, disappears after anti-amebic treatment.

Most patients develop fat intolerance especially when the fat is ingested in rich desserts, milk, and fat meats. The acute distress resulting from a fatty meal in amebic patients is easily mistaken for a cholecystitis, particularly when the hepatic flexure of the colon is the main seat of the pathology.

The intolerance to milk, however, may be caused also by other factors. The enzymatic apparatus of the adult gastrointestinal tract is less well equipped to handle milk than is that of the infant. Our observations lead us to believe that milk allergy frequently develops in prolonged chronic cases.

The necessity of the irritated bowel in amebiasis to be supplied with non-irritating, non-gasforming food is imperative. Indigestible material, such as fibrous vegetables and meats with strong fascias (veal) must be excluded.

In our experience, not only the quality but also the

quantity of the food plays a decisive role. Many high caloric foods must be forbidden or limited. A patient who customarily eats pie with ice cream for dessert obtains approximately 500 calories from this source. When these desserts are forbidden, he will be most reluctant to make up for this loss by eating larger quantities of bread, potatoes, or meat. For this reason, the patient must be encouraged to eat at more frequent intervals.

In searching the literature for reference to diet in amebiasis, little was found except for the diet described by D'Antoni[3] who gives the regimen used by Jones.

This diet was evaluated by one of us[4] in a preliminary publication. Since then, some changes were initiated. At present, the following modification of the D'Antoni-Jones diet is in use by us.

MODIFIED D'ANTONI — JONES DIET

SOUPS

Recommended: pure soups, broth; strained soups: cream soups, pureed vegetable soups; soups with rice, noodles, liver and meat.

Restricted: Vegetable soups.

Forbidden: greasy and spicy soups; soups with forbidden vegetables.

MEATS

Recommended: fowl, lean pork and beef, bacon, liver, game, lamb - preferably boiled, broiled, baked or stewed; ham and tongue.

Restricted. fried meats, salt meats, brain.

Forbidden: smoked, spicy and fat meats; corned beef; veal; sweetbreads; sausages, kidney, mutton.

FISH

Recommended: dry fish, broiled or baked.

Restricted: shrimp, lobster, crab.

Forbidden: oily fish; fish prepared with rich or spicy sauces or oil.

VEGETABLES

Recommended: potatoes, lettuce, carrots, beets, string beans, green peas, egg plant, okra, tomatoes, spinach, squash - cooked, pureed,, strained.

Restricted: turnips, broccoli, cauliflower, sprouts, artichokes, asparagus, alligator pears.

Forbidden: gas-forming and fibrous vegetables as lima beans, lentils, cabbage, sauerkraut, radishes, onions, celery, corn, watercress, endives, peppers, cucumber.

GRAIN PRODUCTS

Recommended: bread, crackers, macaroni, spaghetti, noodles, sago, sorghum, rice, breakfast cereals except bran.

Forbidden: hot breads and rolls, bran.

FRUITS

Recommended: cooked apples and pears.

Restricted: raw oranges, grapefruit, peaches, apricots, cherries, tangerines, guava, strawberries, bananas.

Forbidden: all fruit not listed as recommended or restricted.

BEVERAGES

Recommended: tea, postum.

Restricted: coffee (one to two cups per day), chocolate, milk, (one glass per day if considered necessary), juices as tomato, prune, apricot, pineapple, and orange (diluted if highly acid, one to two glasses per day).

Forbidden: alcoholic beverages, carbonated drinks, juices not listed as restricted.

DESSERTS

Recommended: jello, puddings, gelatin, sherbert — if not rich.

Restricted: custard, cookies, cake, pies, pastries.

Forbidden: syrup, ice cream, and desserts not listed otherwise.

MISCELLANEOUS

Recommended: cottage cheese, salt, butter.

Restricted: dry, hard cheese, eggs, (6 to 8 a week scrambled or poached), cream, (used for breakfast cereals only).

Forbidden: rich and highly fermented cheese, potato chips, nuts, honey, catsup and other sharp seasonings.

SUPPLEMENTS

Vitamins.

During the last four years, six hundred cases of amebiasis were placed on this diet. Many patients objected to the restrictions concerning carbonated drinks, ice cream, and coffee. Some of them found it difficult to understand our objections to milk. Approximately one-half of the patients maintained constipation which, however, was easily alleviated by the use of mucilaginous colloids.

Vitamins were administered parenterally in the beginning. The inconvenience of this technic prompted us to shift to oral vitamin therapy, which proved adequate.

For those patients with marked gaseous distention, various combinations of homatropine methyl bromide, belladonna, papaverine and phenobarbital were found useful.

The subjective complaints generally disappeared after the diet was observed for approximately one month and did not return if the regimen was maintained for an adequate length of time, i.e., one to two years.

This diet was also given to patients with chronic bacillary dysentery, non-specific ulcerative colitis, irritable colon of unknown origin and proved itself as effective as in amebiasis.

SUMMARY

Six hundred cases of amebiasis, belonging to types I to III of Craig, were successfully managed by a modification of the diet of D'Antoni and Jones.

The features of chronic amebiasis, the inadequacies of drug therapy, the importance of dietary treatment and the difficulties encountered in such management were discussed.

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Nutrition Notes

THE IDEAL HUMAN DIET

The medical conception of what constitutes the 'ideal' diet has always been rather dogmatic, but as McLester (1) points out, the conceptions have radically changed almost every decade during the fifty years of modern scientific medicine. We have passed through several 'eras' and now find ourselves adopting the high protein diet, particularly the meat diet, as the ideal one. There is much evidence to support our present faith in the value of the high protein diet, particularly its influence on anemia, liver disease, the globulins of immunity reactions, and so on. Yet it seems unwise to assume that a high meat diet is prefectly immune to criticism, or that we shall always be able to obtain it.

If we are to credit the theories clustered around Seyle's conception of the 'diseases of adaptation', we must tentatively assume that high protein diets sometimes contribute to the development of certain forms of hypertension. It is not yet perfectly clear that sodium is the only offender. This particular problem requires further elucidation. Rice is a low protein product, and in China where it has formed the staple of diet for 4000 years, hypertension was rare until recently. China, as well as India, always had access to 'unrefined salt' which contains about 90 per cent sodium chloride. Are we to assume that the lack of hypertensive disease in China has been due solely to the Chinese temperament, or should we relate it to the low protein diet which has so long been used. Here is an opportunity for the nutritionists and the psychosomaticists to get together. In America where the meat content of the diet is at least very high, hypertension is more common than elsewhere. An energetic investigation of the pre-disease diets of persons with hypertension ought to be undertaken with a special view to determining the protein content of the diets habitually used by these individuals.

It is true that the present belief in the values of the high protein diet and high meat diet seems scientifically well-founded, but we have not yet solved the problem of the total number of calories which an individual ought to consume. It is instructive to recall that observations in World War II both in the conquered and the liberated countries, plainly indicated that even the hardest manual labor could be satisfactorily supported by a maximum of 2300 calories per day. This is an encouraging fact in view of the possibility of the decreasing availability of lavish diets for everyone. Populations are increasing rapidly but the acreage of cultivatable soil is decreasing because of faulty agriculture methods, floods, wind and drought. Probably we shall be gradually driven toward cereal and vegetable proteins to replace much of that which is now supplied by meat. The next 'era' in diet may well be one in which calories are somewhat restricted and the protein percentage elevated by the addition of non-meat proteins. This is so likely to happen eventually, that we ought to undertake experiments in which large scale feeding of populations by the use of cereal and vegetable proteins, are observed over a period of years. We need to learn the effects of such a diet on health, vigor, body weight and immunity to disease. India, where animal protein is unobtainable for the general population, where jungle anemia and hepatic cirrhosis flourish, and where religious interdiction largely prevents the use of meat in any case, should be an ideal setting for such an experiment By arrangement with the government of India, the World Health Organization could begin such an experiment without too great a cost, by utilizing the indigenous peanut (ground-nut), cereals and vegetables, as well as artifically-produced yeast foods. Indian physicians and nutritionists could manage the scientific observations required. The results would be valuable for our own guidance in future wars as well as in peace.

(1) McLester, J. S.: Protein comes into its own J. A. M. A., Apr. 2, 1949, Vol. 139, No. 14, 897-902.

Abstracts on Nutrition

HARPER, M.: *Congenital steatorrhea due to defect of the pancreas.* (Med. J. Australia, Jan. 29, 1949, Vol. 36, No. 5, 137-141).

The author feels that the use of the term 'celiac syndrome' has led to much confusion, and that idiopathic celiac disease should be separated from congenital pancreatic steatorrhea. In the latter disease the stools are bulky, frequent, fatty and oily and the fat may constitute 50 per cent of the weight of the dried feces, of which 60 per cent may be unsplit fat. The child, though of normal weight at birth, loses weight in the first month inspite of eating well. The diagnosis rests at first on the character of the stools. The disease is familial and enquiry should be directed to determine the death of siblings in infancy. Pathologically the pancreas may appear grossly normal, but microscopic examination shows much dilatation and distortion of the acini and ducts, and connective tissue is increased. The author points out that Paige was unable to find any evidence of cystic fibrosis. Emphysema results from the invari-

ably associated respiratory infections, which always cause death. These cases should be overfed, and the ravenous appetite should be satisfied. A feeding high in protein, balanced with carbohydrate, is indicated. Enough fat should be fed just to keep the size and number of the stools normal. Pancreatin is of limited value but should be used. Sulfonamides and pencillin tide the patients over acute respiratory flare-ups but the pulmonary condition must be regarded as incurable and always eventually fatal, usually before nine years of age.

BORNSTEIN, J. AND NELSON, J. F.: *Observations on the effect of high fat diet in alloxan diabetic rats.* (Med. J. Australia, Jan. 29, 1949, 121-126).

The authors conclude from their study of the title subject, that a diet rich in fat ameliorates alloxan diabetes in rats, whether the diabetic state is severe or mild and, if given for long enough periods, results in *permanent amelioration of the disease.* The weight is maintained for only a limited period of time, after which there is a rapid weight loss accompanied by a transient rise in blood sugar level. The urinary output is diminished by the direct action of the fat. Severely diabetic animals are able to utilize fat more readily than mildly diabetic animals. A diet with 40 per cent added fat is the most ketogenic in these rats, ketosis being abolished by elevation of the fat content to 70 per cent. Diabetic rats are able to utilize fat and convert it to glycogen, regardless of the severity of the diabetes. Severely diabetic animals receiving a high carbohydrate intake are unable to deposit glycogen. This suggests that glycogen is produced from intermediate products of fat metabolism. There appears to be an inverse relationship between glycogen deposition and the production of ketone bodies.

RIPPY, E. L.: *Diet in diabetes mellitus.* (Texas State M. J., Jan., 1949, Vol. 45, No. 1, 29-33).

Pre-insulin dietary modes of treatment emphasized the desirability of low caloric intake, and it was realized that starvation days had a beneficial effect on refractory cases. Since insulin it has appeared that glucose is helpful so long as normal blood sugar levels are reasonably maintained. The author does not admire Tolstoi's free dieting, but admits Tolstoi may leave an impression on diabetic treatment by encouraging more liberal diets, though scientifically controlled. Only a few modifications from normal diet are recognized as favoring the diabetic state. The diabetic individual ought to maintain his weight at normal, or slightly less, as he ages. After 40, egg yolk and glandular foods high in cholesterol ought to be limited as they contribute to the development of arteriosclerosis. The patient must be made diet conscious, but "food regulation" is a better term than "diet". *The patient's welfare is not served by the creation of a diet to avoid insulin.*

HENDERSON, P.: *Incidence of diabetes mellitus in children and need of hostels.* (Brit. Med. J., Mar. 19, 1949, 478-479).

The incidence of diabetes is considerably less in Britain than in the U. S. A., in the ratio of 10 to 27 per 100,000 of populaton. In 1948 a survey was made of some 21 urban and rural districts in England. Of 1,307,000 children under 16 years of age living in 16 cities and 5 counties, 183 were known to have diabetes, the majority living in cities or towns. The incidence rose sharply with age. Among children under 5 years only one in 180,000 had the disease, while between 10 and 15 years, one in 3,000 was diabetic. The author discussed the problem of whether such patients are better treated at home or in hostels. Rural children will do best in hostels owing to lack of treatment facilities and the same statement applies to the large numbers of children orphaned by the war, or discommoded by separation of the parents. Some 150 diabetic children in England and Wales ought to receive institutional treatment. About 90 can be accommodated by the two hostels now in existence and a third will be opened in 1949.

NITZULESCU, I., ZOSIN, C. AND BRIUL, E.: *Concerning the existence of a hypoglycemic reflex conditioned by the sensation of a sweet taste.* (Rev. Med.-Chirurg., 1948, 59th year, No. 3-4, 180-183).

The authors' researches give evidence of the existence of a conditioning of insulin secretion, stimulated not only by eating carbohydrates but also by simply a sweet taste or merely rinsing the mouth with a sweet solution. This has interesting possibilities in the dietary treatment of the diabetic. Joslin a long time ago proposed giving diabetic patients a small amount of sugar an hour before meals, hoping thus to stimulate the islets of the pancreas and thus obtain a better utilization of carbohydrates. In the first 5 minutes after "tasting sweet" a mild hyperglycemia occurs followed soon by a hypoglycemia due to increased insulin production.

LEVERTON, R. M.: *Breakfast with high-quality protein.* (Nutrition News, April, 1949, Vol. 12, No 4, page 13).

If even one essential amino acid is absent from the meal being eaten, or is present in insufficient quantity, this deficiency will limit the utilization of other amino acids. When incomplete proteins, which do not contain all of the essential amino acids are metabolized, they supply the body with some of the essential amino acids. These acids, however, are neither used nor stored to be used later when the other essential amino acids are supplied from other food sources but they are oxidized and the nitrogen portion excreted. The authoress quotes Paul Cannon,—"The synthesizing mechanisms operate on an all or none principle and are perfectionistic to the extent that if they cannot build a complete protein they will not build it at all." The authoress reports an experiment on 15 girls who had milk for breakfast for 16 days but no milk or other good protein for breakfast for the next 16 days, the diets being quantitatively the same for each 24 hours. There was evidence that more available nitrogen was used during the period when milk was included in the breakfast than when there was no milk in that meal.

RUTHERFORD, G. T: *Ketonuria in a child with cirrhosis of the liver.* (Brit. Med. J., Mar. 19, 1949, 480-481).

Ketonuria with hypoglycemia in a child of 2½ years of age caused convulsions and coma on several occasions. Drinking glucose water caused improvement. The blood sugar, on one admission to hospital, in coma, was 35 mg. per 100 ml. The urine contained acetone and diacetic acid. He finally died in a convulsion. No liver disease had been suspected but autopsy revealed portal cirrhosis of nodular type. The author feels that the hypoglycemia which caused death was due to liver disease. In this case, however, the absence of ascites, jaundice and wasting shows that the disease was by no means in the last stage Presumably interference with glycogenolysis or glycogenesis was responsible, although the author does not theorize, and merely presents the facts. The pancreas was found normal.

Editorial

DIGESTION AND FEAR

Gastric acidity is known to increase under conditions of chronic fear and anxiety. Hoelzel (1) by continued examination of his own gastric juice at a time when he was under great emotional strain, due to fear, found a greatly heightened plateau of acid production, which returned to normal as soon as he was relieved of the psychic distress. Wolf and Wolff (2) as well as many others have made similar findings on patients or individuals under stress. Others, however, have reported repression of gastric acidity under fear and anxiety, and these include Beaumont's observations on Alexis St. Martin. Mahl (3) in an experiment on 7 dogs, found that 6 of them regularly responded to fear and anxiety by increased gastric acidity but one of them did not. Mahl assumes that this particular dog probably developed an acute emotional response but not a chronic one, to the electrical-and-buzzer form of stimulation used. None of the dogs, incidentally, developed peptic ulcers or indeed any pathological tissue changes.

When a convict receives and eats a hearty breakfast one or two hours prior to execution, as many of them do, autopsy has usually shown, grossly at least, an absence of digestion, and the whole breakfast is ordinarily found in the stomach. Cannon's hypothesis that the incretion of adrenalin, under conditions of acute fear, while mobilizing glucose from the liver, also stopped the vegetative process by supressing gastric juice, in order to conserve bodily energy for the flight-or-fight effort, is not questioned, but Mahl's excellent experiment certainly makes it seem necessary to draw a distinction between the effects of acute fear and chronic fear on the gastric acid production. The fact that one of his 7 dogs failed to react to chronic anxiety might be presumed to depend on 'temperament' which, as a genic contribution, continues to introduce into clinical medicine as well as experimental medicine an unpredictable factor. Further dog experiments are needed, and it would also no doubt prove valuable to conduct more extensive gastric examinations on human beings under stress. Hypnotically induced fear states may perhaps lack something that real fear states possess. It is not always easy to be sure that a given individual is really experiencing a chronic anxiety state and for this reason care must be exercised in selection of subjects and they ought to be sufficiently psychoanalyzed to determine the nature of their anxiety if possible. A set of overt circumstances, such as impending academic examinations among students, or the uncertainties of livelihood in those of marginal economic status, may be presumed to set up an anxiety state yet on examining the individual we may discover that he or she is not worrying very much even though worry might seem appropriate. The subjective element is of far greater importance than the life situation. It is also probably true that even in cases when a definite anxiety is present there is the possibility that worry and fear may not always take the 'gastric' form of expression. Alexander has emphasized this point many times. Consequently such a clinical experiment ought to be prefaced by a more or less careful analysis of the individual or else, as in Hoelzel's case, the work carried out by the physician on himself at a time when he is aware that he is actually in an anxiety state. In our psychosomatic approach to ulcer we ought to remember, as Mahl indicates, that as yet we are dealing with somewhat loose probabilities when we assume that a psychic state of fear is the primary etiological factor in ulcer production, because we have yet to see an objective union of the emotion-acidity-ulcer elements, although we cannot avoid assuming that they are united.

Beaumont S. Cornell, M.D.

1. Hoelzel, F.: Fear and gastric acidity. Am. J. Digest. Dis, 9: 188, 1942.
2. Wolf, S. Wolff H. G.: Human gastric function. New York, Oxford Univ Press, 1943.
3. Mahl, G. F.: Effect of chronic fear on the gastric secretion of HCl in dogs. Psychosom. Med. Jan.-Feb. 1949, Vol. XI, No. 1, 30-44.

ERRATA

In the September issue in the article "Studies on Serum (Carotene) in Man", it has been requested that some of the Authors' degrees be indicated. — SUSAN KANN, Ph.D., ALICE P. MAURER, A.B., and HARRY SOBOTKA, Ph.D. We regret that the correct character for "micrograms" was not used by the printer.

Book Reviews

Food Facts for the Diabetic. By Joseph H. Barach, M.D., F.A.C.P., Oxford University Press, 1949, New York, N. Y., $4.00.

Recently Dr. Barach placed the profession under obligation by publishing an unusually practical, succinct yet comprehensive work on "Diabetes and its Treatment." The same publisher now offers to the diabetic himself an equally valuable handbook which probably covers all that any diabetic needs to know in order to treat himself intelligently, along with his physician's assistance. Dr. Barach neither minimizes nor exaggerates the difficulties encountered by the diabetic individual, although the text inspires optimism, as it undoubtedly ought to. The author gives reasons why a diabetic ought not to smoke or drink alcohol and it is hoped that these observations may exert due influence on the patients who read the book. Fake remedies are enumerated. More than half the book is occupied with specimen diets. In this section the patient would be able to find exactly the diet ordered by his physician. This book is highly recommended for patients.

How to Become a Doctor. By George P. Moon. 130 pages, ($2.00), The Blakiston Company, Philadelphia, Pa., 1949.

As Dr. A. C. Ivy, in the foreword states, "it is obviously important that students planning a career in one of the health professions obtain correct information regarding the details surrounding admission to a professional school . . . Mr. Moon, for the first time, provides students and advisers with sound and accurate inside information regarding many important but frequently forgotten matters, any one of which may make the difference between acceptance and non-acceptance." Reading this book is like sitting down with an authority and discussing a future career in medicine, dentistry, veterinary medicine, pharmacy, optometry, chiropody, occupational therapy, hospital administration, medical illustration or science. Since every conceivable angle of the subject is fully covered, the book might well be recommended by physicians to young men and women who desire to enter medicine.

General Abstracts Of Current Literature

CLINICAL MEDICINE

BOWEL

GOTTLIEB, C., SHARLIN, H. S. and PECK, W.: **A roetgen finding of unusual interest in perforation of the colon.** (Radiol., March 1949, Vol. 52, No. 3, 359-362).

Two cases are described in elderly patients in which it was possible to make a diagnosis of colonic perforation from the x-ray findings. In both cases colonic obstruction was present, due to carcinoma. The perforations occurred proximal to the malignant lesions and were large, permitting massive extravasations of the fecal material into the peritoneal cavity. In neither case was any appreciable amount of air present in the peritoneal cavity. The fact that the fecal shadows did not conform in outline to that of the colon was the point of importance in making a diagnosis of perforation.

CLARKE, A. M.: **Intestinal obstruction in infants.** (Med. J. Australia, Feb. 19, 1949, 225-228).

The author enumerates and describes the various forms of intestinal obstruction met with in infants and describes also the chief surgical methods of treatment, as well as collateral means of support, including gastric suction, oxygen inhalations for abdominal distention, chemotherapy, etc. He makes the point that it is not necessary to make a pre-operative diagnosis of the cause of the obstruction, but it is extremely essential that obstruction should be diagnosed at the earliest possible moment and laparotomy undertaken. "It is always better to look and see than to wait and see."

MILLER, T. G.: **Intestinal intubation.** (Cleveland Clin. Quart., April 1949, Vol. 16, No. 2, 68-73).

One of the perfectors of intestinal intubation (Miller-Abbott tube) gives an instructive address on the subject which covers the early period in which the Netherlands physician, Scheltema, passed a mercury filled tube through the intestinal tract of a child, and in which Max Einhorn developed his "duodenal pump" and later his jointed tube for bowel intubation (1919). The double-lumen tube with attached balloon was developed by the author and Abbott after 1930. It was found that duodenal contents have an average reaction of about pH6, while at lower levels it became neutral. The osmotic pressure becomes the same as that of the normal tissue fluids (300 milliosmoles) at lower levels, due to the chloride and bicarbonate content. The introduction of glucose into the small gut pushes the osmotic pressure above normal, but this is accompanied soon by a drop in the chlorides, in order to obtain a more or less fixed osmotic pressure. Little sugar is absorbed from the stomach but with an artificially blocked pylorus, its concentration is reduced by an outpouring of gastric juice to increase the volume. An enormous amount of sugar can be absorbed in the duodenum. No matter how high the glucose content may be in the stomach, it is reduced to 6 per-

cent on reaching the jejunum. The Miller-Abbott tube has finally elucidated the mechanism of the "dumping syndrome" seen following gastric resections. Hypertonic solutions fall directly from the stomach into the jejunum calling forth an enormous outpouring of fluid into the jejunum in an attempt to bring the concentration down to the proper level. It is the over-distention of the jejunum which causes distress and nausea. Hyperglycemia results from the effort to absorb excess sugar rapidly. Diarrhea results from dispersion of the material throughout the tract in order to bring it in contact with a larger absorptive surface so that sugar can be more quickly absorbed. Management consists simply in withholding food from the patient in a hypertonic state or delaying its admission to the jejunum. Narrowing the stoma may be required. The idea that antiperistalsis develops when the bowel is obstructed is erroneous. Fecal vomiting is not due to antiperistalsis, in obstruction, but to the development of a central current or flow backwards as a result of pressure against the point of obstruction. Morphine produced at first a spasm of the bowel followed by a more prolonged period of relaxation. Hence morphine ought not to be used in bleeding peptic ulcer because relaxation militates against closure of the bleeding vessels. Machella has devised a method, using the tube, by which nourishing food may be placed in the small bowel and all residue reaching the terminal ileum removed, thus sparing the colon activity. By use of an amigen-dextrimaltose mixture gratifying results have been obtained in most cases of ulcerative colitis.

WRIGHT, L. T. and STRAX, S.: **Pyoderma grangenosum in chronic non-specific ulcerative colitis treated with aureomycin.** (Harlem Hospital Bull., 1:99, Dec. 1948).

Pyoderma gangrenosum is a very severe pyogenic cutaneous complication of ulcerative colitis. Staphylococcus, streptococcus, B. proteus, B. pyocyaneous, and B. coli are the most common bacterial invaders. Aureomycin produced a dramatic response in both skin and colon in a case treated by the authors. An extensive, chronic pyogenic, necrotizing lesion of the skin which had begun at the site of an injection, occurred in a woman who had suffered from ulcerative colitis for seventeen years. Her general condition was extremely poor and neither the pyoderma nor the colitis had responded to intensive medical treatment.

Ileostomy was performed as a life-saving measure, but there was gradual deterioration in her general state. Prompt colectomy was considered imperative. She was given aureomycin pre-operatively. Ferrous iron was the only other medication.

Within one week, drainage from the bowel and from the skin lesions had stopped. Healing (with scarring) was almost complete in one month and there was improvement in health, weight and appetite. No toxic effect was noted. Resection of the colon was successfully performed and the patient is now active and in good health.

MORROW, A. W.: **Present concepts in ulcerative colitis.** (Mar. 26, 1949, Vol. 36, No. 13, 403-450). Med. J. Australia.

The author believes the specific cause of ulcerative colitis still is elusive, but he recognizes a sub-group due to a streptococcus, not, however, the diplo-streptococcus of Bargen. The bacillary dysentery theory is not acceptable and there is no good evidence of a viral cause. Allergy may be important. He regards neurogenic factors as of secondary importance. The fact that the mucolytic enzyme, lysozyme, is increased seventy-five times above normal is striking and it may turn out that the disease is due to an overproduction of this enzyme by emotional disturbances. He favors the usual symptomatic treatment, with which all are familiar. Total intravenous alimentation for as long as 13 days rests the colon, but the diarrhea resumes as soon as oral feedings are again commenced. Medical ileostomy by means of the double-lumen Miller-Abbott tube for as long as two weeks, sometimes induces a remission.

CULLEN, P. K.: **Embryogenic megacecum complicated by volvulus.** (J. Ind. State Med. Assn., May 1949, Vol. 42, No. 5, 415-419).

A male aged 39 was admitted to U. S. Naval Hospital, Great Lakes, June 28, 1943 with a distended and painful abdomen and constant vomiting. X-ray films revealed distended colon and a diagnosis of obstruction was followed by laparotomy at which a possibly unique finding was made. A huge cecum, without any appendix, 16¼ inches in length was obstructed by a volvulus below the ileo-cecal valve. It was removed and patient made an uneventful recovery. It would appear that the appendix is not, in man, the atrophic vestige of the embryonic cecum but that it is the remains of an organ to which no present function can correctly be attributed and that it is possible to have an embryological reversion to a primitive state. What the author has termed "embryogenic megacecum" probably is the creation of an unusual embryological developmental anomaly of the infantile cecum and vermiform appendix. It has no relationship to Hirschsprung's disease.

LINBERG, G. and MORALES, D.: **Treatment of acute intussusception by an enema of roentgenologic contrast medium.** (Am. J. Dis. Child., March 1949, Vol. 77, No. 3, 303-309).

In 18 consecutive cases of acute intussusception during the first 3 years of life, conservative treatment by means of an enema of roentgenologic contrast medium has proved very successful in the author's hands. Most of these cases were treated within a very few hours of the time that the ob-

struction occurred. By the use of a barium enema the colon is visible and pressure is exerted orad at the point of obstruction. When the lesion resolves, it can be both felt and seen to give way and the patient experiences immediate relief. In some cases ether anesthesia was necessary to obtain proper relaxation. Some cases had to be operated on, and in these there could be found no evidence of injury from the previous manipulations of the bowel.

HAYES, H. T. and BURR, H. B.: **Cancer of the rectum and colon: analysis of private cases, 1926-1946.** (Texas State J. M., April 1949, Vol. 45, No. 4, 198-201).

This report covers 401 cases of cancer of the colon and rectum seen in private patients from 1926 to 1946. For growths in the right colon, resection of this colon with end-to-side transverse ileocolostomy is recommended. For growths elsewhere in the colon, open end-to-end anastomosis without colostomy is suggested. For rectal growths, anterior resection without colostomy when possible, otherwise an abdominoperineal resection. Adequate preparation for surgery includes at least a week of colon irrigations, daily laxatives, sulfathalidine in recommended doses, low residue diet, adequate whole blood before and during operation and attention to vitamins and blood proteins.

PENNINGTON, G. A.: **Ulcerative colitis: clinical features, diagnosis and treatment.** (Med. J. Australia, Mar. 26, 1949, Vol. 36, No. 13, 405-409).

History and physical examination are important in diagnosis. He discusses the fact that the personality profile in this disease is rather characteristic. He emphasizes the toxemia, malnutrition, anemia and intestinal manifestations and notes the complications, but fails to mention the dermatological or ocular manifestations. Medically, he favors treatment by means of chemotherapy, diet and blood transfusions. Ileostomy to be followed by colectomy is advised if there is progressive deterioration despite medical treatment.

DUNLOP, E. E.: **Ulcerative colitis: the ileostomy life.** (Med. J. Australia, Mar. 26, 1949, Vol. 36, No. 13, 399-403).

The author says that ileostomy may be the price some patients with ulcerative colitis must pay for life. Ileostomy, moreover, may be more tolerable than continued severe colitis or proctitis. An ileostomy artificial anus can be made with small risk in patients whose condition is not desperate prior to operation, and with modern management, a cheerful and useful economic and social existence is possible.

LEISHMAN, A. G.: **Idiopathic ulcerative colitis with severe ulceration of the skin and peritonitis.** (Proc. Royal Soc. Med., Feb. 1949, Vol. XLII, No. 2, 105-106).

A woman, aged 42, had had remittent diarrhea for 10 years, and severe ulceration of the legs. Eight years previously she had been admitted to hospital with a severe relapse of diarrhea, general edema, albuminuria, and x-ray evidence of an enlarged heart and chronic ulcerative colitis involving the whole colon. Appendicostomy and colonic irrigation did not improve the diarrhea, but her edema disappeared, not to return. Three years previously she developed a small indolent ulcer on the dorsum of the left foot which persisted for 6 months. Two ulcers were now present on the right and one on the left leg above the ankle, the largest measuring 6 inches by 4 inches and extending round the posterior surface. Considerable cellulitis and inflammatory edema extended up to the thigh. There was marked anemia and the colon showed much polyposis. The liver was enlarged and liver function tests abnormal, so that cirrhosis was suspected. The leg ulcers required 6 months to heal. She later developed peritonitis, which, following incision, drained for 4 weeks. Following this, improvement was steady with relief of anemia and partial control of the diarrhea.

The possibility of hepatic cirrhosis was suggested also by the failure to restore the albumin-globulin inversion on a high protein diet. The period of edema, albuminuria and cardiac enlargement was thought to be due to anemia and hypoproteinemia, but there was a possibility of its being due to a vitamin B deficiency. The peritonitis was very little affected by chemotherapy, but the author does not refer to other agents than penicillin. Healing of skin ulcers (pyoderma gangrenosum) usually coincides with general improvement in the colitis. Epithelial hypersensitivity may be present in such cases. (Cultures from the skin ulcers were sterile or showed Gram-positive cocci of low viability. Swab from the colonic ulcer showed Staph. aureus, Strep. fecalis, and Ps. pyocyanea).

PANCREAS

MUETHER, R. O. and KNIGHT, W. A.: **Pancreatic dyspepsia.** (Miss Valley Med. J., Mar. 1949, Vol. 71, No. 2, 49-52).

Abnormal serum amylase determinations are frequently encountered in patients with abdominal pain and dyspepsia, indicating a disturbance in pancreatic function. The serum amylase levels vary considerably in this group and a single determination is frequently inadequate. The **prostigmine amylase test** will frequently demonstrate alterations in pancreatic function when other methods fail. Transient disturbances in pancreatic function with rapid return to normal have been demonstrated in patients. Medical treatment consists in small frequent feedings, avoidance of alcoholic beverages, avoidance of excessive fats, with the use of antispasmodics and sedatives. Pancreatin in fairly large doses combined with small doses of prostigmine may be useful in some cases. The use of defatted whole duodenal extract is under study and appears to have some promise.

BOWERS, J. M.: **Carcinoma of the body and tail of the pancreas.** (Northwest Med., Jan. 1949, Vol. 48, No. 1, 42-46).

The author points out that cancer of the head of the pancreas causes symptoms secondary to duodenal obstruction and blockage of the common bile duct, while the early symptom of carcinoma of the body and tail of this organ is a dull, persistent pain located high in the abdomen and often in the middle of the back. In cancer of the body and tail, we meet with progressive and rapid loss of weight, constant anorexia, persistent and unexplained diarrhea, altered carbohydrate metabolism, enzyme secretions and important roentgen and gastroscopic signs. If these points are kept in mind, preoperative diagnosis may be made more often, and early cases may prove amenable to surgery.

LIVER AND GALLBLADDER

COLBERT, J. W.: **Pruritus in acute hepatitis.** (Bull. U. S. Army Med. Dept., Dec. 1948, Vol. VIII, No. 12, 954-955).

In 75 patients with acute hepatitis, 16 experienced generalized pruritus in the absence of primary dermatological disease. More than 50 percent of the patients noted the itching before the 10th day and 15 of the 16 patients developed pruritus as the jaundice was increasing. In most cases the itching subsided rather promptly after the icterus reached its peak and began to subside.

ROTOR, A. B., MANAHAN, L. and FLORENTIN, A.: **Familial non-hemolytic jaundice with direct van den Bergh reaction.** (Acta Med. Philippina, Oct.-Dec. 1948, Vol. V, No. 2, 37-46).

While familial jaundice usually is considered hemolytic in type, a non-hemolytic form has already been described by various authors and referred to as "constitutional hepatic dysfunction," "hereditary hyperbilirubinemia" or "familial cholemia," etc. All hepatic functions, with the exception of bile pigment metabolism are normal, and the jaundice is of the non-obstructive type, the serum giving the indirect van den Bergh reaction. The author, however, presents two instances of familial non-hemolytic jaundice, one of which was traced through three generations, in which the jaundice was of the obstructive type and gave the direct van den Bergh. There was no bilirubinuria, no signs of obstruction, and no evidence of disease of the liver could be histologically demonstrated. The condition is compatible with life and health and suggests that further knowledge is required with respect to the total metabolism of bile pigment.

MISCELLANEOUS

STABLE, G. AND PHILPOTT, I. G. *An epidemic of gastro-enteritis in infants with special reference to treatment.* (Med. J. Australia, July 17, 1948, Vol. 35, No. 3, 63-69).

In 1947 a severe epidemic of gastroenteritis occurred in Brisbane, 384 infants being admitted to the hospital. Half the cases and most of the deaths were caused by *Salmonella bovis morbificans.* The death rate, at the height of the epidemic was 40 per cent but was lowered to 3 percent by treatment. Most cases occurred among artifically fed infants. Therapeutic diets found most effective were a sequence of 5 per cent solution of glucose or sucrose in water, whey, whey-modified milk, and modified milk. In severe cases, intravenous treatment with half-strength normal saline solution and 5 percent glucose solution was required. Deaths occurred from starvation and hepatic intoxication until casein hydrolysate was given as well. Serum therapy was of little value. Salmonella septicemia occurred in severe cases. Streptomycin in doses of 25 to 50 mgm. every 3 hours intramuscularly was most effective in toxic salmonellesis stages but had no effect on entero-colitis.

CURTIS, G. M., CONNOR, A. C. AND SWENSEN, R. E.: *Propyl thiouracil in the management of complicated hyperthyroidism.* (Ill. Med. J., Sept., 1948, Vol. 94, No. 3, 161-166).

Three cases are described, representing three kinds of complications which may be associated with hyperthyroidism, (1) diffuse hyperplastic goiter with impending cardiac failure, (2) recurrent hyperthyroidism in which the patient refused surgery, (3) primary hyperthyroidism, the management of which was complicated by a sensitivity to iodine. In the first case, the use of propyl thiouracil provided the long time interval of control during which the cardiovascular system recovered to the point where surgery could be performed without undue risk. For the patient refusing surgery, the drug provided a remission. In the third case, sensitive to iodine, it proved an alternate form of pre-operative therapy.

GILBERT, J. A. L. AND DUNLOP, D. M.: *Diabetic fertility, maternal mortality and foetal loss rate.* (Brit. Med. J., Jan. 8, 1948, 48-51.)

While the use of insulin has increased the fertility of diabetic women and made pregnancy a relatively safe procedure for the mother, it has failed to produce any significant decrease in the fetal mortality rate in diabetic mothers. It was found by an analysis of the obstetric histories of 165 women in whom diabetes was diagnosed between the ages of 25 and 69, that prior to the onset of the disease, the overall fetal loss rate was twice the non-diabetic control rate. In patients in whom diabetes was diagnosed before the age of 45, the pre-diabetic fetal loss rate was three times the non-diabetic control rate. The maximum pre-diabetic fetal loss rate, which was six times the control rate, occurred in the two years immediately before the diagnosis of diabetes was made, and was as high as that observed after the onset of clinical diabetes. There appeared to be no relation between the severity of the ensuing diabetes and the pre-diabetic fetal loss rate. The onset of clinical diabetes may be a late stage in some general metabolic disturbance, an early feature of which is a high fetal loss rate.

Increase In Peptic Ulcer Of The Aged

by

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PEPTIC ulcer after the age of 60, may be acute and primary, or it may be chronic, recurring and secondary to other conditions. The diagnosis of gastric ulcer at this age may not only be difficult but is of the utmost importance, since early cancer of the stomach may ulcerate and give ulcer symptoms. Peptic ulcer has formerly been considered to occur infrequently in elderly people, but in the past few years it has been reported more frequently and its importance emphasized by many authors.

A review of the American literature of the last 9 years, in which the ages of the patients are given, is presented in tabular form, and the number above the age of 60 years is indicated. A few articles on peptic ulcer of soldiers are not included because of their younger selected ages. Articles concerning only those above the age of 60 are also not included. The incidence of deaths from peptic ulcer of the aged in Cedar Rapids from 1940 to 1948 inclusive and the cases of peptic ulcer admitted to St. Luke's Hospital in the past 10 years are presented.

Kiefer and McKell[1], have recently emphasized the difficulty of making a diagnosis of peptic ulcer in the aged and have noted the frequency of complications and the difficulty in the management of many of these elderly patients. Marshall and Welch,[2] like many others, believe that the treatment of gastric ulcer is surgical. They found in a series of 26 malignant gastric ulcers, that 23 percent were above the age of 60, and in a series of 105 cases of benign gastric ulcer, that 22.8 percent were above the age of 60. Hence the age of the patient is of very little diagnostic aid. Meyer and Saphir[3] and Boles and Dunbar,[4] have found from necropsy material that peptic ulcer of the aged may be acute or chronic, and secondary to a variety of other diseases and conditions.

In a review of the literature by the author,[5] in 1940, where the ages were given, it was found that 10.5 percent of 4079 cases of peptic ulcer were above the age of 60. In the present review, the incidence of peptic ulcer in those beyond the age of 60, varies from 5.5 to 37 percent in clinical cases, and as high as 53 percent among the deaths from peptic ulcer. The high death rate for those above the age of 60, indicates that the present management of this disease in these cases is not as successful as in the younger patients. Ivy[6] has stated that before 1900, very few duodenal ulcers were reported from autopsies, but as present they are more frequent than gastric ulcer. Jennings,[7] has found a marked increase during the past 150 years in the incidence of peptic ulcer in older people and in men. He says that between 1850 and 1900, of every 6 perforated ulcers, 3 were in women under 25 years old, one in an elderly woman, and one each in a young and aged man. Since 1920, of every 10 perforated ulcers, 1 was an elderly woman and 9 were in younger or middle aged men.

In Tables I to V, there is presented the number of cases studied by the authors. The number and percent of those above the age of 60 are also given in these tables.

TABLE I

Incidence of Perforated Peptic Ulcer after Age 60.

Author	Total Cases	Age above 60 No.	%
McCleery, R. S., Jackson Mem. Hosp. Bull II No. 1:45, 1940	100	13	13
Hagood, M.M., J. Med. Assoc. Georgia, 33: 12, Jan. 1944	36	2	5.5
Black, B. M., and Blackford, R. E., Surg. Clin. N. Am., Aug. 1945, p. 918	96	16	17
Anderson, R.H., Allen, G.L. and Packard G.B., Rocky Mt. Med. J., 42:661, Sept. '45	59	11	18.6
Olson, H. B., and Norgore, M., Ann. Surg. 124: 479, Sept. '46	166	42	25.3
Thompson, H.L., and Prout, H., Arch Surg. 54: 390, April 1947	91	13	14.2
Totals	548	97	17.7

TABLE II.

Incidence of Bleeding Peptic Ulcer After Age 60.

Author	Total Cases	Age above 60 No.	%
Rafsky, H. A., and Weingarten, M. J. J. A. M. A., 118: 5, Jan. 3, 1942	408	56	13.7
Schiff, Leon, S. Med. J., 37: 335, June, '44	160	34	21.
Totals	568	90	15.8

TABLE III

Incidence in Surgical Treated Peptic Ulcer After 60.

Author	Total Cases	Age above 60 No.	%
Miller, T. G., and Nicholson, J. T. L., Am. J. Med. 1: 476, Nov. 1946	113	19	16.8
Wangensteen, O. H., The Jour. Lancet, 66: 31, Feb. 1946	13	3	23.
Sanchez-Vegas, J., and Collins, E. N., Am. J. Med. Sc., 211:428, April '46	30	5	16.6
Vinci, V. J., Speight, H. E., LaBelle, L.D. and Buckley, W F., Conn. State Med. J 10: 281, April 1946	9	2	222
Colp, R., and Drukerman, L. J., Ann. Surg. 124: 675, Oct. 1946	8	2	25
Smith, R. C., Ruffin, J. M., and Baylin, G. J., S. Med. Jour. 40: 1, Jan '47	50	4	8
Bartels, R N., and Dulin, J. W., Surgery			

21: 496, April, '47	100	22	22
Bradshaw, H. H., and Hightower, F., N. Carolina Med. J. 8:204, April '47	98	12	12.2
Marshall, S. F., and Welch, M. L., J. A. M. A., 136:748, March 13, '48	105	24	22.8
Totals	526	93	17.6

TABLE IV

Incidence of Medically Treated Cases of Peptic Ulcer After Age 60

Author	Total Cases	No. Age above 60	%
Sanchez-Vegas, J., and Collins, E. N. Am. J. Med. Sc., 211:428, April '46	20	7	35
Vinci, V. J., Speight, H. E., LaBella, L. D. and Buckley, W. F., Conn. State Med. J. 10: 281, '46	21	4	19
Wood, M. N., Am. J. Digest. Dis. 14: 1, Jan. '47	58	14	24
Levin, E., Hamann, A., and Palmer, W. L. Gastroenterology 8: 565, May '47	24	1	4.1
Feldman, M., Am. J. Med. Sc., 215:13, Jan. '48	112	29	25.8
Rafsky, H. A., Weingarten, M., and Krieger, C. J., J. A. M. A., 136: 739, March 13, 1948	1800	378	22.2
Pollard, H. M., Block, M., Backrack, W. H. and Mason, J., Arch. Surg. 56:372, March '48	28	2	7.1
Mulsow, F. W., St. Luke's Hospital, Cedar Rapids, Ia. 1940 to 1948 inclusive	435	139	31.9
Totals	2498	574	22.9

TABLE V

Incidence of Death from Peptic Ulcer After Age 60

Author	Total Deaths	Age above 60 No.	%
Rafsky, H. A. and Weingarten M. See Table II	36	16	44
Meyer, J., Sorter, H. K., and Necheles, H. J. A. M. A. 120: 813, Nov. 14, 1942	8	3	37
Thorstad, M. J., Surg. 12: 964, Dec. 1942	22	5	22.7
Hagood, M. M., See Table I	4	0	0
Schiff, Leon, See Table II	11	3	27
Anderson, R. H., Allen, G. L., and Packard, G. B., See Table I	18	6	33
Olson, H. B., and Norgore, M., See Table I	46	18	39
Gibbs, J. O., Quart. Bull. Northw. U. Med. Sch., 20: 328 Sept. '46	219	86	39
Miller, T. G., and Nicholson, J. T. L., See Table III	3	1	33
Bartels, R. N., and Dulin, J. W., See Table III	8	4	50
Thompson, H. L., and Prout, H., See Table I	15	3	20
Meulengracht, E. (Bleeding Cases) Arch. Int. M. 80: 697 Dec. '47	26	13	50
Mulsow, F. W., Deaths from Peptic Ulcer Reported at City Hall, Cedar Rapids, Ia. from 1940 to 1948 inclusive	72	50	69
Mulsow, F. W., Deaths at St. Luke's Hospital from Peptic Ulcer, 1940 to 1948 Inclusive	29	21	72.4
	517	229	44.2

Peptic Ulcer in St. Luke's Hospital, Cedar Rapids, Iowa.

During the past 10 years, there has been discharged from this hospital 435 patients with peptic ulcer. The site of the ulcer, the sex, and ages above 60 are given in Table VI. Those which had been reported as gastroduodenal or obstructing are included with the duodenal ulcers in this table. The diagnosis in these cases was made by x-ray, surgical exploration or necropsy. 32 percent of the gastric ulcers and 31 percent of the duodenal ulcers were in patients over 60 years old. The ratio of male to female was 3 : 1 for both gastric or duodenal ulcer.

TABLE VI

	Cases	Male	Female	Above age 60. Cases	Male	Female
Gastric Ulcer	174	132	42	56	41	15
Duodenal ulcer	261	196	65	83	62	21
Totals	435	328	107	139	103	36

TABLE VII

Peptic Ulcer Deaths in St. Luke's Hospital

	29 Cases — Male	Female	Above age 60. Male	Female
Gastric Bleeding	2	3	2	3
ulcer Perforated	7	0	4	0
Duodenal Bleeding	4	2	4	0
ulcer Perforated	5	2	3	1
Obstructed	4	0	3	0

The number of cases in Table VII is small, but like the others, show that hemorrhage is the most common cause of death in the older group of patients and perforation more frequent in the younger ages. Also death from hemorrhage is higher in females and perforation higher in males.

TABLE VIII

Deaths from Peptic Ulcer in Cedar Rapids

	Total	Male	Female	Above age 60. Total	Male	Female
Gastric bleeding	23	17	6	18	15	3
" perforation	19	18	1	10	9	1
Duodenal perforation	6	4	2	2	2	0
Bleeding peptic,	12	9	3	9	6	3
Obstructing peptic	12	9	3	11	8	3
TOTALS	72	57	15	50	40	10

In Table VIII it will be seen, from the death certificates filed at the City Hall in Cedar Rapids, that 69 percent of the deaths from peptic ulcer were in people above the age of 60. Among the women 60 percent of the deaths were due to hemorrhage, and 66 percent of these were above the age of 60. In the men 30 percent of the deaths from peptic ulcer were due to hemorrhage, and 80 percent of these were above the age of 60. Perforated peptic ulcer caused 20 percent of the deaths of women and 38 percent of the deaths from ulcer in men. And 10 percent of the women and 26 percent of men were above the age of 60 in this group. In the deaths from obstructing ulcer 90 percent of the men and all of the women were above the age of 60. Those above the age of 60 accounted for 90 percent of the deaths from obstruction, 77 percent of the deaths from hemorrhage, and 48 percent of the deaths from perforation of a peptic ulcer.

Discussion

From a review of the literature and the exam-

ination of the death certificates at the City Hall in Cedar Rapids, Ia., it appears that peptic ulcer is increasing in older people, faster than the percent of older people are increasing. Kiefer and McKell,[1] have stated that 10.8 percent of the white population of the United States is above the age of 60. In Tables I, II, and III, it may be seen that 17 percent of all perforated, bleeding and surgically treated cases of peptic ulcer are above the age of 60 years. The reports of the medically treated cases in Table IV, give 22.9 percent of the patients above the age of 60. Table V reveals that 44 percent of all deaths from peptic ulcer occur in those over 60 years old.

These figures are all much higher than they were a few years ago. DeBakey,[8] found in a review of 6875 perforated peptic ulcers reported in the literature, 7.46 percent were above the age of 60. His figures were concerned with reports before 1940. In a review by the author,[5] in 1940 it was found that 10.5 percent of the 4079 reported cases of peptic ulcer, were above the age of 60. But in the present review since 1940, those above the age of 60 amounted to 20.9 percent of all cases. Among 65 deaths from peptic ulcer in Cedar Rapids before 1940, there were 38 percent above the age of 60. But in 72 deaths since 1940, there were 69 percent above the age of 60.

Reports from other countries also indicate the recent increase in peptic ulcer in older people. Forty,[9] in a report of 100 cases of perforated peptic ulcer in England, found that 21 percent were above the age of 60. Linn,[10] in southern Australia found in 763 chronic cases of peptic ulcer that 30 percent of the gastric ulcers and 19.6 percent of the duodenal ulcers occurred in those above 60. In 159 perforated ulcers he found 20 percent of the gastric and 14 percent of the duodenal ulcers in those over 60 years old. In 74 acute peptic ulcers he found 17.5 percent above the age of 60. There are other recent reports which indicate the increase in the incidence of peptic ulcer in elderly patients.

There are many factors which may be involved in this increasing incidence of peptic ulcer of the aged, but until more is known about the etiology of this disease we cannot explain completely the increase in the older people. A few of the more apparent important factors are presented below.

1. The fact that more people are reaching the older ages, no doubt accounts for some, but not all of the increase.

2. Those in the older age group are subject to more of the serious complications and therefore require hospitalization. It is such cases that form a large percent of the cases reported in the literature. Hence a higher incidence in older people.

3. The failure of home management also accounts for a larger number being admitted to hospitals. Many of these older patients are admitted to hospitals for surgical treatment which would not have been attempted a few years ago.

4. The diagnosis is often more difficult and they are admitted to hospitals for further and more accurate study. The diagnosis between gastric ulcer and gastric cancer often requires surgery and microscopic examination. By the more accurate diagnosis in these older patients, many formerly reported as cancer are now found to be ulcers. Hence we have the increase in gastric ulcer and the decrease in gastric cancer.

The above factors may be more or less relative, but a few of the more primary causes for the increase are the following:

5. Some years ago when the daily work of more people depended upon physical fitness, the older people automatically retired to less energetic forms of life. People formerly were considered to be too old to do hard work after 50 years of age. Today many people beyond the age of 60 or 70 engage in exhausting physical and nervous types of work, recreation or vacations. These strains tend to disturb the eating habits and circulation of the older people more than in the younger people.

6. Another factor which has been impressed upon me in recent years is, the large number of these elderly people who have many missing teeth or poorly fitting false teeth. Among 28 cases there has been 13 who had poorly fitting dentures and 5 who had many missing teeth. Most of these eat very little or no meat, because of their inability to properly masticate meats or fear of eating it. The deficiency of proteins has been found to slow the progress of wound healing in dogs, and this may be a factor in peptic ulcers not healing, in many such patients.

7. Other factors which may be of importance are: the increased use of alcoholic drinks, carbonated soft drinks and the increased use of sugar, coffee and tobacco in women.

Conclusions

The incidence of peptic ulcer in those beyond the age of 60 years appears to have increased in recent years. A few of the more important factors in this increase have been presented. In a review of the recent American literature on peptic ulcer, where all ages are considered, there were 19.2 percent above the age of 60, among 3705 cases reported. In 416 deaths from peptic ulcer reported in the literature, 38 percent were above the age of 60. Among 65 deaths from peptic ulcer in Cedar Rapids before 1940, there were 38 percent above the age of 60, but in 75 deaths from peptic ulcer since 1940, 69 percent were above the age of 60 years.

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A Newer Concept Of Arthritis And The Treatment Of Arthritic Pain And Deformity By Sympathetic Block At The Sphenopalatine (Nasal) Ganglion And The Use Of The Iron Salt Of The Adenylic Nucleotide.

"THE DYNAMICS OF MUSCLE TONUS"

PART IV.

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FROM the three preceding sections of this work it can already be seen that the problem of muscle spasm and the manifold disturbances arising from it in the skeletal muscles, cardiac muscle and myofibrils of the vascular tree are all amenable to sphenopalatine treatment both through the sympathetic nervous system at the sphenopalatine ganglion directly and through the use of adenylic nucleotide indirectly.

In this work I am presenting the concept that arthritis is a form of dystrophy due to disturbed function of the sympathetic nervous system associated with disturbance of muscle tonus and that the accompanying joint and bone changes are secondary to the muscle spasm. The sympathetic nervous system which plays a dominant role in muscle tonus is also associated with the biochemical changes in calcium and water metabolism. The frequent association of so-called arthritis with lumbo-sacral spasm (sacro-iliac), cervico-thoracic (frozen shoulder and stiff neck) and spinal (Marie-Strumpell Disease) follow a uniform pattern of muscle spasm, joint changes with or without fluid, and decalcification with small free calcific deposits. That this is not a matter of infection of the joints I have been repeatedly able to demonstrate by the almost immediate disappearance of both signs and symptoms of the so-called arthritis by treatment of the sympathetic at the nasal ganglion. While infection of the joints as part of a general septicemia occurs such as following sinus thrombosis, gonorrhea, syphilis, etc. this is not the common picture which the physician and layman classify as arthritis. A more precise conception must be given to the condition commonly called arthritis and I propose that the form associated with muscle spasm be called "arthritic sympathetic dystrophy" and definitely delineated from joint involvement of infectious origin.

It might be said that focal infection of teeth, tonsils, and sinuses have frequently been associated with arthritis and that removal of these foci is commonly followed by improvement. In an earlier paper entitled "The Neurologic Aspects of Nasal Sinus Infections," I pointed out that it was not the bacterial agent itself that was transported to the distant locus which caused the remote pathology but the reflex neurologic disturbance which could, through the sympathetic nervous system, induce remote biochemical changes. While Pickworth was able to demonstrate the passage of organisms along the nerve sheath from the nasal sinuses to the intracranial structures, it is unlikely that such a mechanism would prevail in remote joint changes.

It can therefore be seen that a correct diagnosis of joint disturbances must include an evaluation of the etiologic factor and the commonly admitted failure of the customary therapy must be considered as unsuccessful because it was not based on a proper conception of the underlying mechanism. When a patient who has been treated unsuccessfully for months for an acute sacro-iliac pain and

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arthritis of the hip by casts, traction, diathermy, short wave, etc. receives immediate and continued relief within a few minutes by treatment of the sympathetic at the nasal ganglion and when he no longer requires any further care, it must logically be admitted that the cast, traction, diathermy, etc. is incorrect therapy based on a wrong conception and that treatment of the sympathetic was correct.

In one of the cases here reported, Miss G., patient of Dr. Massie Page of Washington, the x-ray report indicated almost total loss of joint cartilage in the acetabulum and the roentgenologist volunteered the opinion that "this patient will never walk" The patient was able to walk after one week of daily treatment, discarded her fancy aluminum crutches and is now able to take dancing lessons. In the case of Dr. Reiss who had an arthritis of the right knee with acute flexion for several months, several nasal ganglion treatments gave striking relief. However, one of his orthopedist friends prevailed upon him to put the leg in a cast. After three months in the cast the leg was in greater flexion than when he started and in addition, his quadriceps femoris showed definite atrophy. Dr. Reiss then returned for nasal ganglion treatment and in a period of two weeks recovered almost 100 percent extension.

Still another case is that of Dr. Henry M., attending orthopedist of a leading orthopedic hospital. He suffered from an acute left "frozen shoulder" and came in severe pain after trying the customary treatments for several days. Treatment of the sympathetic at the nasal ganglion gave him immediate relief and after three daily treatments was quite well and required no further treatment. About a week later he telephond me that he had a policeman with a sacro-iliac condition and would I tell him how to give the nasal ganglion treatment. I frequently get such telephone calls for instruction which I consider equivalent to calling an abdominal surgeon and asking for instructions to do a gall bladder operation. The correct treatment of the sympathetic requires a knowledge not only of the regional anatomy which varies considerably with the changes in the lateral nasal wall, but also a knowledge of the pharmacology of the alkaloids since a number of the alkaloids may be used with great precision and the possible reactions must be known and promptly recognized. Unless one has received proper instruction the results may be haphazard and unfair to the procedure. The pharmacologic management of the sympathetic will bear the same relationship to the surgery of the sympathetic that propylthiouracil does to thyroid surgery. Its proper administration should be taught in all medical schools.

The direct treatment of the sympathetic at the sphenopalatine ganglion should also be supplemented by correction of the biochemical deficiencies as herein described. This has afforded so much greater relief to the arthritic patient with such rapid profound improvement in the local condition of the joints that it is also deserving of the most careful attention.

Dr. Russel Cecil has seen some patients of the series of cases here reported. These patients who came crippled and deformed and who had the best of modern treatment were then in a few days or weeks able to walk and carry on in comfort.

In adopting the newer concept of arthritis as a sympathetic dystrophy we can better understand the rationale of the treatment. From the almost immediate response resulting from the relief of muscle spasm, it can be postulated that polyarthritis is a disturbance in muscle tonus with secondary joint changes incident to immobilization. Disturbances in water and mineral metabolism and circulatory changes contribute the local joint pathology that meets the eye on inspection but the deranged muscle metabolism surrounding the joint and peripheral vascular spasms are the true offenders. To study polyarthritis one has to understand as comprehensively as possible all the factors involved in muscle spasm. To do this we must retrace our steps in the previous sections of this work and again devote ourselves to a study of the nerve impulse to the muscle, the discharge of muscle energy and the restoration of muscle energy incident to muscular contraction and relaxation. Were polyarthritis not a disease of muscle tonus it would not be possible to take a deformed arthritic hobbling on crutches and have her walking freely in a few minutes. That the sympathetic nervous system plays a vital part in the pathologic physiology of polyarthritis is clearly shown.

In the case of Mme. de V., a severe polyarthritic patient who was under the simultaneous observation of Dr. Russel Cecil and myself, very dramatic progress was made during her treatment of the sympathetic at the nasal ganglion and the injections of iron adenylate (Ironyl) and calcium ascorbate (Calscorbate). The oedema of the joints of the hands, wrists and ankles had almost completely disappeared after a few weeks of treatment. Her sedimentation rate had dropped from over 75 to 35. One day she received a letter telling her that royalties on a patent left by her husband would be discontinued. That evening the swelling of her joints reappeared, the hands became cold, painful and clammy. The wrists and ankles also were swollen and tender, quite like her original condition. Her energy left her and she again complained of fatigue. Under treatment of the sympathetic she recovered promptly and was again able to resume her activities.

In this case the recurrence of polyarthritis had all the earmarks of shock induced by fear. A biochemical basis for this pathologic physiology could be traced to the relationship of thyroxin or iodine to the breakdown of the pyrimidine nucleus of the adenylic nucleotide and the disturbance of this energy producing complex. This phase was described in my paper "Mechanism of Nephrosis in Sinusitis in Children," read before the Third International Pediatrics Conference in London, 1933.

With free motion of the joints the swelling of the joints and the shiny coldness of the extremities disappear along with the pain and sensation of stiffness. Almost in a matter of minutes these changes became visible. As far back as 1926 Greenfield Sluder made it a practice to visit with me in New York each year for a week so that together we could discuss and study these manifestations of the sympathetic nervous system. Just before he died in his last letter to me he wrote, "I should like to live in New York City and work with you, this field is so enormous."

While Sluder had made observations on the relationship of the sphenopalatine ganglion to hemicrania and lower half headache, he did not correlate the wider aspects of the sympathetic with sacro-iliac and low back pains, arthritis, or the peripheral circulatory spasm with the sphenopalatine ganglion. He gave me full credit for these contributions and urged me to continue publishing these observations despite the discouraging resistance on the part of the profession generally. I remember one occasion that was particularly distressing. I had been invited to read a paper on the sphenopalatine ganglion in 1934 to the American Society for Regional Anaesthesia. In the course of the presentation I described the relief of sacro-iliac and low back pain by anaesthetization of the sphenopalatine ganglion. As I proceeded I noticed the chairman becoming very restless and at the conclusion

of the paper he arose and announced that there would be no discussion of this paper but that a business meeting would be held and all those who were not members would kindly leave, myself included. I did not know at that time that the chairman then proceeded to ask the Society to pass a vote censuring me for insulting the intelligence of the members by asking them to believe that one could relieve a sacro-iliac pain of years standing in a few minutes by anaesthetizing the sphenopalatine ganglion.

As luck would have it, this very chairman had a severe attack of sacro-iliac pain three years ago and in desperation was induced to come to me for treatment. After a few minutes of sphenopalatine treatment he was so completely relieved that with tears in his eyes he begged forgiveness for his past sins and pleaded with me to teach him the technique. Although he was not a rhinologist I gave him sufficient instruction to tackle at least the milder cases. Recently he was able to publish a series of cases in the New York State Medical Journal reciting a number of sacro-iliac and low back pain cases relieved by sphenopalatine ganglion therapy. It will probably take many more such instances before the profession becomes fully aware of the great usefulness of treatment of the sympathetic at the sphenopalatine ganglion. This work laid the basis for the use of procaine intravenously or locally injected into the painful area, used as described by Graubard and Peterson. These local injections are necessarily less effective than the direct treatment of the sympathetic at the nasal ganglion. More recently the use of procaine ascorbate intravenously has been employed with relatively good results. This effect would also operate through the sympathetic as here described but again is much less profound than the nasal ganglion approach.

During the intervening years the collateral sciences of chemistry, physics and mathematics have come forward with many of the explanations that were then so eagerly sought. The field of enzyme chemistry unfolded the action of the vitamins. The field of physics contributed a newer understanding of the nerve impulse and presented an intensely interesting analogy to electrical circuits in the servomechanism or feed-back system that tells us much about the mechanism of the continuous action of the nerve impulse.

Finally mathematics was coralled to give us more precise information of the physiology of the negative feedback system that makes the nervous system tick both in time and action. The work of Norbert Wiener of the Massachusetts Institute of Technology and Arturo Rosenblueth of Harvard, has demonstrated the collaboration of the mathematician and the physiologist. It is through such correlation that we are finding, as Canon called it, a "physiological factor for a physiological defect."

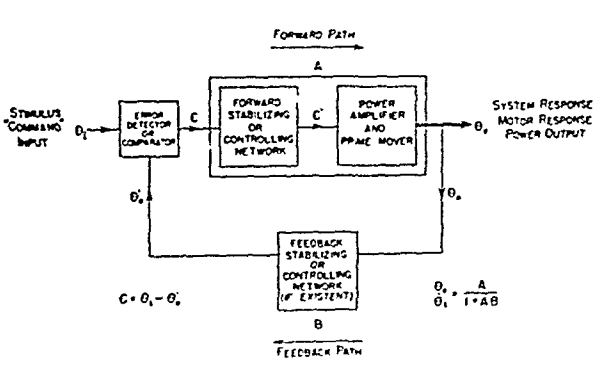
Also in this period I had the privilege of coordinating two chemical streams of research. One was the chemistry of nucleic acid which in a paper entitled "The Mechanism of Nephrosis, etc." read before the Third International Pediatric Conference in London, 1933, I described the intermediate metabolism of nucleic acid and pointed out the role of the adenylic nucleotide in energy metabolism. The other was the later studies of Szent Gyorgi ,Englehardt and others, showing that the muscle fibril was composed of two proteins, actin and myosin, which together with the highly phosphorylated adenylic nucleotide (A. T. P.) and inorganic ions calcium and magnesium reproduced muscle contraction in the test tube. They also showed that in muscular contraction energy is spent and that for relaxation fresh energy has to be supplied through the adenylic nucleotide system. This I had already proven through the clinical use of the adenylic nucleotide. I had by experience found that the iron salt of the adenylic nucleotide was more effective than the acid or sodium salt and that the adenosine mono-phosphoric derived from yeast had a greater peripheral vascular effect than the adenylic derived from muscle. I had already also demonstrated that the iron adenylate actually supplied muscle energy and was dramatically effective in controlling fatigue. I thus had laid the ground work for the work that followed on muscle energy. All of this made possible an enormous step forward in correcting muscle spasm since it became obvious that an additional supply of fresh energy through the administration of the adenylic nucleotide was supplying a "physiological factor for a physiological defect."

To find an explanation for the phenomenon of sudden correction of years long pathological conditions by influencing the sympathetic at the nasal ganglion, I had to study the anatomy and physiology in the light of biochemistry and physics. To do this I had to school myself in both departments these many years. The biochemical approach consumed most of the time of the investigation and gave considerable valuable data in explaining the disturbance.

This was still a far cry from the control of a spastic myofibril because the discharge of the adenylic system is a function of the shift of the inorganic ions, K, Na, Ca and Mg and this, I have shown, is under the direction of the nerve impulse.

The rhythmic flow of impulses (or we can say electrons) from the sympathetic nervous system presents us with the problems of a continuously acting electrical circuit which can be treated either as a linear circuit or a sinusoidal one. In order to secure such rhythm the system must be a circular one, that is, a feed-back system whereby the current that returns regulates also the variations in supply. When a lag occurs or any alterations arise we get either greater stability or instability of the system depending upon the direction of the alteration.

Let us look at an example of an electrical system presented by Donald Herr. This will help us understand the physiological one in the nerve impulse.



1. An example of a simple feedback system commonly occurring in nature and in certain engineering applications, with basic elements delineated (Courtesy of Mr. DONALD HERR, Allen-Bradley Co., Milwaukee, Wisconsin.

FIGURE No. 1

We see from this picture that a disturbance in the feed-back would place the whole system on either a higher or lower level. This is precisely what we would expect in a spastic or flaccid muscle. What the factors are that could effect such shift we will find in the enzyme chemistry that handles the nutrition of the muscle, that is, the capacity to release energy for phosphorylation of the adenylic system.

While the illustration describes a simple feed-back system in which only one feed-back loop exists between output (response) and input (stimulus), more complicated

systems involving several or many complex feed-back paths would be subject to the same conclusions as these simple ones.

It is found that when the nature and amount of the feed-back are adjusted to give greater stability, then the system becomes more sluggish and relatively inaccurate in its response. Conversely when the nature and amount of the feed-back are adjusted to give greater accuracy and rapidity of response, then the system rapidly approaches a condition of instability of one kind or another.

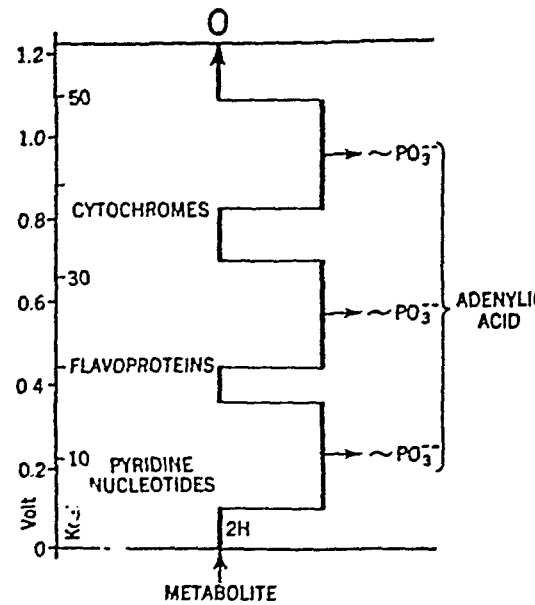
Herr points out in the electrical field that accuracy of response and stability of operation appear as two absolutely interdependent, yet contrary attributes to the feed-back system. In servomechanism work, we have to compromise degree of stability to satisfy the accuracy-of-response specifications depending upon the controlling requirements in a particular application. Physiologically we have the same findings when we compare the action of thyroxin and the alert, frequently brilliant slightly unstable hyperthyroid patient with the action of phenobarbital or the sluggish methodical unemotional hypothyroid patient.

L. A. MacColl of the Bell Telephone Laboratories emphasizes that decreasing the amplification of the amplifier tends to diminish the speed and accuracy of the system and decreasing the amplification sufficiently to make the system satisfactorily stable may result in making the system so sluggish and inaccurate as to be worthless. Such is also the case in the heart muscle and coronary occlusion where phenobarbital and morphine may complete the inability of the heart muscle to function by decreasing the amplification of the nerve impulse. In a previous paper, Part II of this group, I have shown that supplying the adenylic nucleotide with its energy rich phosphate both serves as an amplifier and quickly corrects the poorly acting heart muscle and is a more logical therapy for heart failure. The detailed rationale is described in Part III of this series.

Going back to our electrical examples, MacColl states that "sometimes the necessary modifications of the system amount to nothing more than changes in the values of certain passive elements such as inertias, stiffnesses and resistances. In other cases the necessary modifications can be best effected by introducing additional passive elements. In still other cases, it may be necessary to introduce subsidiary feed-back loops."

In pharmacology we have passive elements that may be introduced to modify such feed-back systems particularly of the sympathetic nervous system. In this group are the alkaloids which nature has already provided in its own biochemical systems. Many of these form the backbone of therapeutics such as quinine which lowers the metabolism, atropine which regulates amplification of nerve impulses, cocaine, novocaine, pontocaine and the group of sensory anaesthetics, muscarine, curare, eserine, and prostigmine. It is also interesting that these drugs also modify the reactions of cocaine quite in opposite fashion to prostigmine.

Beutner has shown that substances which influence electropotential difference stimulate the tissues in the smaller doses. He indicated that the action of highly toxic substances operate by causing electrical changes. This would tend to be borne out by the changes in electron potential between the pyridine nucleotides, flavoproteins and cytochromes as indicated in the following chart by Lipmann.



—Transformation of Electron Potential into Phosphate Bond Energy.

FIGURE No. 2

As a further demonstration, Beutner constructed a model biological electric cell as follows:

— Hg	KCl solution saturated with HgCl	Nitrobenzene and 10% oleic acid	Physiological saline with 0.02% sodium oleate alkaloid added here	KCl solution saturated with HgCl + Hg

The normal electromotive force of this cell without any alkaloid added is approximately 85 mv. The change in electromotive force produced by adding the indicated amounts of alkaloids is given below.

Substance	Mg/100 cc.	Decrease in e.m.f.,mv.
Pilocarpine	1	33
	2	43
	5	57
	10	69
Atropine Sulphate	0.2	7
	1	25
	2	40
	5	57
	10	71
Strychnine Sulphate	0.1	4
	0.2	9
	0.5	18
	1.0	31
Cocaine HCl	0.2	10
	1	49
	5	94
Quinine HCl	0.5	4
	1	11
	2	17
Morphine Sulphate	1	0
	2	6
	5	11
	10	18
Caffeine	0.5	1
	2	2
	10	4

Acetylcholine produces a negative potential of 200 mv. Beutner concludes that electrical potential differences in tissues have a vital function and naturally any foreign chemical which modifies the normal potential difference, or rectifies an abnormal electromotive force, is bound to show drug action. Complete inhibition of all these forces is a general property of all narcotic substances. We thus see that a conception of electron phenomena is essential in both physiology and pharmacology.

Just as in electrical circuits, the introduction of collateral factors influences the output, so also in the treatment of the sympathetic slight changes in combination of the alkaloids produce rather large differences in stability. The local anaesthetics while slowing the rate and degree of impulses permit an increase in the mechanical efficiency of the muscle. Thus an arthritic with spastic musculature unable to lift his legs to walk up the stairs will immediately after sympathetic block at the nasal ganglion promptly walk up and down stairs even if he had been unable to do so for years. The collateral use of atropine, prostigmine, or curare will profoundly influence the degree and type of response. When such a patient also receives an injection of the iron salt of the adenylic nucleotide (Ironyl) mixed with 1 cc. of an injectable B-complex, the energy response is truly dramatic. For home use the coenzymes of the B-complex and amino acids (Co-amino) continue the energy supplementation. The catalytic effect of iron is increased by the home use of iron ascorbate (Ferro-C). Such a regimen has produced the results described in the case histories.

It is necessary now to consider what caused the dysfunction of the muscle to lead it to spasticity. This is a question similar to that confronting an engineer in an electrical circuit. Here a study must reach down from the hypothalamic seat of the sympathetic nervous system and the pituitary and its intimate relationship with the olfactory structures described in an earlier paper on the "Neurologic Aspects of Nasal Sinus Infections" to the structures of the spinal cord.

In the spinal cord the differently myelinated fibres present factors similar to that of variations in insulation and one of the theories of causalgia is the spread of nerve impulses in relatively mild nerve injuries from partially demyelinated or unmyelinated fibres to other pathways. Disturbances in nerve sheath insulations would cause disturbances in the normal feed-back arrangement with either an exaggeration of the effect registered as pain or diminished effect as anaesthesia or loss of useful function. The feed-back must be a negative one.

If we carry our feed-back system still farther as an example we find that Wiener and Rosenblueth attribute purposeful physiological behavior to a negative feed-back system and claim that "the intrinsic disease of negative feed-back is one and all that they cease to be negative. This state may be enforced by compelling them to operate at other frequencies than those for which they were proportioned, or may be permitted by altering the natural period or increasing the amplification of the signal. As soon as feed-backs operate with a gain greater than one they cease to subserve their proper ends."

The influence of bacterial and virus infections as well as drugs must play such altering influences on normal negative feed-back systems. Lorente de No' already recognizing this feed-back idea as a basic factor in the understanding of nervous system behavior, stated, "We are certain that, in the nervous system activity does persist in closed circuits of neurons, is responsible for nystagmus persisting long after stimulation has ceased and may account for a very active memory in which the occurrence of a certain event may be retained without reference to the instant of occurrence." The psychiatric significance of this statement and its relationship to the sympathetic nervous system cannot be overemphasized.

It is also to such feed-back system arrangements that we must come to explain the almost instantaneous correction of a longstanding muscle spasm. The direct influence of the medication in the amplification of nerve impulses, permitting a correction of a disturbed feed-back system leading to a recovery of longstanding disease condition, offers a logical and well substantiated explanation. This approach also opens up a new capacity for the treatment of diseases and presents new angles of attack. It provides a new concept applicable to arthritis and spastic states and the basis for my concept of arthritis as a "sympathetic dystrophy of the joints and muscles."

As a precise example of its application we find that in arthritis, Lovgren was able to demonstrate a high citric acid blood level. Taken by itself it does not convey much information but when considered from the feed-back angle we find that citric acid is an important member of a feed-back cycle whereby the energy is secured from the breakdown of carbohydrates for the eventual rephosphorylation of the energy rich adenylic to the triphosphate state necessary to produce the energy to relax the contracted state of the muscle fibril. The cycle is described in detail later.

Lovgren also found that arthritics had a low blood serum iron. However, when viewed from the angle of the role of iron in the cytochrome systems we again have a typical feed-back arrangement calling for correction. Through empirical channels Lovgren found what I had already described that the adenylic nucleotide is of primary importance to the arthritic and that the iron atom was important. I had already recommended the iron adenylate (Ironyl) in actual therapy. While he uses a crude mixture containing about 50 percent A. T. P. that is the triphosphorylated muscle adenylic acid, I found after working with both muscle and yeast adenylic that after injection both have a similar capacity for conversion in the body to A. T. P. This was confirmed also by the Memorial group of Brown, Roll and Plentl with tagged adenylic. The yeast adenylic is far less costly and has in some respects a more sustained action. Its action in hypertension seems to be better than A. T. P. In fact, while A. T. P. does not seem to influence hypertension, the yeast adenylic, adenosine 3 phosphoric acid specifically, lowers the diastolic blood pressure as described in the previous paper.

Another observation which puzzles Lovgren and other observers is that arthritics suffering from acute jaundice experience considerable relief from pain and the swelling of the joints. This had led some investigators to actually induce liver damage to secure this effect on the arthritic patient. However, in the light of our feed-back conception, the role of an increased bile level would exert an inhibitory effect on hyalouronidase and thus tend to relieve swelling and pain. It is the hyalouronidase system that here needs attention and is another example of a physiological feed-back system.

In considering the low blood serum iron level in arthritics, I was led to use the iron ascorbate because here we have another striking example of a feed-back system with a direct influence. Ascorbic acid activates arginase which increases the urea formation cycle of arginine-citrulline-urea, thus aiding in controlling water metabolism. Iron depresses the blood serum ascorbic acid level. In arthritis the tendency to oedema is already great. The administration of ferrous sulphate could, by depressing the serum ascorbic acid level, impair the arginine urea cycle and lead to still more oedema. By supplying the ferrous ascorbate (Ferro-C) this untoward effect can be avoided. Besides, the iron ascorbate is much better tolerated than other iron salts as shown by Pijoan, Friend, Heilmeyer, Glanzman, Fleischhalker and others.

The modern handling of an arthritic patient calls for a systematic check-up of the feed-back systems no different than the check-up of a radio. Thus we want to know the blood adenylic level. Larson in 1942 estimated blood adenylic at 0.5 mg. per ml., thus there is 2500 mg. adenylic in 5 liters of blood, most of the adenylic acid being in the red blood cells and much less in the serum. Ruskin and Katz observed the chemical relationship between the red cell, white and hemoglobin level to adenylic. Rothmann also showed the relation of adenylic to hemoglobin level. The fall in sedimentation rate as related to adenylic was described in the preceding section of this series. The blood citric level feed-back system must be checked just as well as the albumin-globulin cycle and the iron-ascorbic acid feed-back mechanisms.

In the "Mechanism of Nephrosis" article in 1933, I pointed out that the oedema, associated with increased serum globulin and inversion of the albumin-globulin ratio, was accompanied by a lowered blood serum iron. I also pointed out the biochemical relationship that tied these factors up to the low adenylic and suggested nucleotide therapy. In nephrosis this treatment proved so successful that I was able to apply nucleic acid and nucleotide therapy for the relief of chronic oedema of the nasal mucosa and the oedema of arthritic joints. Lovgren's findings of high blood serum globulin in polyarthritis thus confirms my earlier work. He also found that polyarthritics who had been helped by adenylic nucleotide therapy showed a drop in the elevated blood serum globulin and elevation of the albumin to a normal albumin-globulin ratio. In my treatise on the "Mechanism of Nephrosis" I showed the biochemical rationale for this occurrence. Larson (1942) showed that the nucleotide level in total blood was lower than normal in polyarthritics.

While this chemical data is so illuminating we must also tie it up with the nerve impulse and the factors influencing the sympathetic nervous system since both mechanisms are involved in arthritis and muscle spasm.

In an earlier paper, "The Neurologic Aspects of Nasal Sinus Infections," I pointed out that remote disturbances such as muscle spasm and arthritic changes are due not merely to the toxic products of infection generally but also to direct influences on the sympathetic nervous system. It was the only way to explain instantaneous relief of muscle spasm following blocking of the nerve impulses from infected sinuses.

More recent laboratory experiments described by Livingston as well as Speransky support my early hypothesis. This was the experimental demonstration of facilitation. "In this experiment rhythmic stimuli from an induction coil are applied to the posterior tibial nerve of a spinal cat. The strength of the stimulus is adjusted until it is just sufficient to produce a reflex contraction of the tibialis muscle. The minimal contractions of this muscle are recorded on a slow moving drum. The phenomenon of facilitation is now shown by applying a variety of mild cutaneous stimuli to distant parts of the cat's leg. For instance rubbing the side of the cat's foot with a wooden applicator or blowing air strongly across the fur of the foot will cause an immediate and marked increase in the magnitude of the contraction taking place in the tibialis anticus. That these strong contractions cannot be directly ascribed to the cutaneous stimulation alone, can be shown readily by stopping the induction coil shocks, whereupon the muscle contractions promptly cease. With the resumption of the rhythmic shocks, the facilitation of the flexion reflex continues as long as the light cutaneous stimulation is maintained. As soon as it is stopped the reflex contractions of the muscle return to their former minimal type of response."

In addition to this mechanism of facilitation, Gasser has shown that the spinal cord can contribute a mechanism susceptible to disturbed nerve impulses. This is the concept of the "internuncial pool." "This is the pool of neurons within the spinal cord, interposed between the posterior horn and the motor pools of neurons in the anterior and lateral horns. Within the internuncial pool, the incoming volleys of impulses are spatially and temporally dispersed before they activate the motor neurons. In addition to the dispersion of impulses, the internuncial pool acts as a switching and coordinating center which determines the routing of impulses to and from all parts of the central nervous system."

Gasser stated, "A given stream of afferent impulses over a peripheral nerve follows one pathway in the centers at one time and another pathway another time. The direction of the switching is conditioned by the situation obtaining at the moment and is always consonant with a coordinated reaction of the whole organism;" and "anatomical peculiarities of the form and arrangement of the endings differentiate the ease of transmission spatially, and the nature of the previous activity differentiates it temporally;" "ultimately excitation in a pool of neurons is dependent upon everything which is taking place in the nervous system anywhere because of the direct representation of this activity in the population of endings in the pool." Thus, for example, a chronic focus of infection could disturb motor function and synchronization.

One of the best examples of the interruption of a self perpetuating nervous impulse is that of the case of Mr. I. M., a patient of Dr. Henry Ross, who had a severe case of Herpes Zoster Ophthalmicus which left him with a continuous sensation of itching and crawling of the left side of his scalp and forehead. If he scratched he had, in addition, a burning sensation. This condition persisted for a year and a half despite a wide variety of treatments at some of our most noted institutions. A single treatment of the sphenopalatine ganglion and anterior ethmoidal nerve gave instantaneous and lasting relief. In this case one could postulate that a rearrangement of the nerve feed-back mechanism had been accomplished since no other treatment was employed. The alteration in nerve function extended far beyond any possibility of the effect of the therapy continuing locally on the nerve mechanism.

Speransky has also shown experimenally that inflamatory processes produced around the nerve sheathe of one leg will induce inflamatory reaction in the approximate location of the contralateral leg. Thus it can be seen that an infected nasal sinus or infected tonsil could induce an increased degree of muscle tonus which would tend to deplete the A. T. P. reserves of the muscle group so overstimulated and lead to muscle spasm.

It has been a very common experience that arthritic conditions have, from time to time, been relieved by removal of focal infection in the teeth, tonsils and sinuses but in many instances this recovery has not followed. In these cases the question arises whether an adequate biochemical improvement has been established whereby the necessary energy for muscle relaxation has been supplied and whether the feed-back system of the nerve impulses has been adjusted so that normal nerve impulses can reach the spastic muscle. The prompt and dramatic relief of arthritics who had had successful removal of foci of infection but had continued to suffer arthritic pain and disability is fairly conclusive of the importance of these two collateral factors.

The elimination of the mechanism of undesirable facilitation of nerve impulses; interrupting a self sustaining feed-back system; supplying the adenylic nucleotide necessary for relaxation of the muscle fibre; furnishing the vitamin coenzymes for correct metabolism; and improving the catalytic activity of increased blood serum iron as well as increased calcium does seem to present a rational and successful treatment of the arthritic patient.

In Parts I and II of this series of papers it was pointed out that muscle spasm is part of the general picture of energy utilization. If we are to postulate that arthritis is a muscle spasm disease we must simultaneously look to those processes that produce energy for the muscle cell as well as the mechanisms of the nerve impulse.

The metabolic process patterns have been masterfully presented by Fritz Lipmann (see illustrations 2 to 5). These dove-tail remarkably well with the electrical conception of the feed-back system already described (see figure 1).

In the study of the metabolic processes of the living cell, Cori and Cori and others have clearly shown that the steps involve a multitude of substances containing phosphate in special energy linkages. A clear connection was shown between phosphate cycles and transformation and transport of energy. In all the cells a chemical network of energy distribution, the adenylic nucleotide system occurred and carried in the form of special energy rich phosphate bonds standard portions of energy, amounting to about one-fiftieth of that liberated by total combustion of a mole of carbohydrate. Thus catabolism consists to a marked extent in the conversion of potential energy of foodstuffs into directly utilizable phosphate bond energy and through alternate attachment and release of energy rich phosphate bonds, catabolism and anabolism are knit together into a largely reversible reaction in continuity. In effect this series of metabolic steps leading to free energy could be compared to the gasoline in an automobile. A muscle fibril in spasm is like a car needing gasoline. If the energy for relaxation is supplied the myofibril will again be in a position to travel and do work. It may also be necessary to start it in low power to secure an additional mechanical advantage. Analagously supplying the energy rich adenylic system may in some cases also require influencing the nerve impulse through the treatment of the sympathetic nervous system at the sphenopalatine ganglion. While this latter procedure may not always be necessary there are cases where the combined effects must be used.

Let us now look at those energy cycles that have already been discovered and explained. The chemical steps in cell fermentation and respiration were previously partially described. The objectives of these steps were to produce power and the nature of the end product could be considered as incidental. The simplest fermentative process, that is, the conversion of glucose into lactic acid and phosphate bond energy, is represented by Lipmann in the following diagram. The reaction sequence is as follows:

hexose/2 ← ~ ph
ph glyceraldehyde + ph
ph glyceryl ~ ph -2H→ ~ ph
ph glycerate - H_2O
ph ~ enolpyrunate→ ~ ph
pyrunate + 2H
lactate

The terms ~ ph, -ph and ph characterize respectively the energy rich phosphate bond (12 K cal), the ester phosphate bond 3 K cal and inorganic phosphate.

SCHEME I

The Process Pattern of Lactic Acid Fermentation

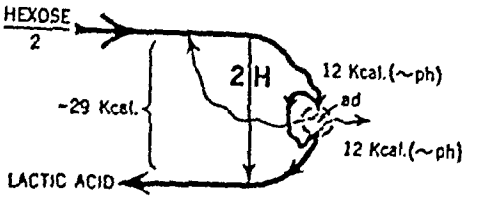


Figure No. 3

This scheme also shows that an initial investment of part of the ultimate energy release returns as induction energy to make the fermentative process autocatalytic. In this cycle a hydrogen donor after unloading of phosphate bond energy is transformed into a hydrogen acceptor. To accomplish this the citric acid cycle jockeys the carbohydrate through its breakdown so that two electrons are repeatedly emitted supplying the potential energy ready to be used as energy rich phosphate bonds. In other words carbohydrate reacts grossly like a mixture of carbon dioxide and molecular hydrogen.

$$(CHOH \cdot H_2O)_X = (CO_2 \cdot 2H_2)_X$$

Another scheme of Lipmann's shows how electron potential transformed into phosphate bond energy.

SCHEME II

A Catalytic Transformer of Electron Potential into Phosphate Bond Energy

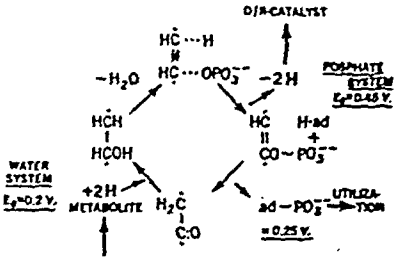
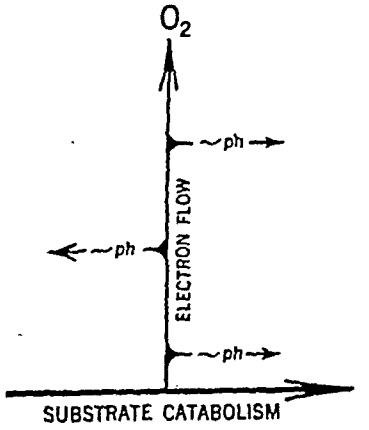


Figure 4-5

SCHEME III

Summarizing Flow Scheme of Respiratory Energy Turnover



Thus the three or four transformers which are built into the pathway of the hydrogen electrons should be considered as the actual power generators of the living organisms. Exchange of adenylic acid hydrogen for the phosphate

group delivers 12,000 calories into the cell and the residual product may be rehydrogenated. Thus the basis of energy in the muscle cell in the last analysis all comes down to the adenylic nucleotide system taking two electrons from the carbohydrate and surrendering it for heat and work in the cell. This is oxidation of the carbohydrate. Originally oxidation meant combination with oxygen; today we consider the removal of one or two electrons as oxidation without necessarily the intermediation of oxygen. After its oxidation a molecule has been deprived of one or two electrons (figure 4).

It is especially fortunate when theory can be supported in practice. The following case records represent only a small number of the extensive series of cases treated.

Thus we find that thinking in terms of the basic sciences helps us both in understanding disease and makes it possible to strike out in an entirely new direction with the most gratifying results. We are now able to scientifically coordinate various disease manifestations not merely by semantics but by biochemistry and physics.

Since submission of this article for publication the results reported with Cortisone have called attention to the role of the adrenal cortex in arthritis. The response to Cortisone is so similar to that of the treatment of the sympathetic at the nasal ganglion that the question arises whether treatment of the sympathetic stimulates hormone E formation and its relationship to the adenylic system.

CONCLUSION

1. A new concept of polyarthritis as a "sympathetic dystrophy" is presented.

2. The prevailing dystrophy could be designated either as arthro-dystrophy or musculo-dystrophy.

3. The correct rationale for treatment becomes clear and points to correction of sympathetic nervous system disturbances and energy inadequacies in muscle metabolism.

4. These disturbances are amenable to treatment through the sympathetic nervous system at the nasal ganglion, the use of the iron salt of the adenylic nucleotide (Ironyl), iron ascorbate, and the coenzymes of the B-complex and amino acids (Co-amino).

5. The disturbances hitherto considered as incurable such as arthritis deformans, Marie-Strumpell's Disease, and advanced polyarthritis, have been sucessfully treated by this new therapy following the new concept. More recently longstanding poliomyelitis disabilities have also shown dramatic improvement under this type of treatment.

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SUMMARY OF CASES (Nurse Ruth Carnahan)

Case 1—M. B., age 50; Female—Polyarthritis

HISTORY

Patient had pain in left knee and both hands with swelling and deformity. Onset 2 years ago with swelling of right ankle. Pain and difficulty in walking. Tires easily. At times patient unable to bear weight on foot. Left wrist swollen and knuckles of left ring finger and thumb. All joints at times show swelling. Both knees and right ankle now swollen. Unable to put her hands behind her, or elevate them.

TREATMENT AND RESULTS

1 ganglion treatment given every day for 3 consecutive days. Patient able to tie her apron and comb her hair. Had not been able to do this for last 6 months. Patient then given 1 treatment each week for 6 weeks. Comes to office alone and by subway, climbing steps and walking 3 blocks without becoming tired and with no pain. Patient under treatment once every month.

Case 2—L. F., age 65; female—Polyarthritis

HISTORY

Began having severe pain in left hip 2 months ago radiating to knee. Unable to stand erect or put weight on foot. Had been hospitalized for 9 days with traction. Spica then applied and she was discharged from hospital. Patient wore spica for 10 days but was very uncomfortable, in extreme pain constantly. Hospital diagnosis was osteo-arthritis of left hip and sacro-iliac region.

TREATMENT AND RESULTS

After 1st ganglion treatment patient was greatly relieved. Able to stand erect and bend easily. Treatment given each day for 3 days then 1 each week for 2 weeks. Patient walking, climbing steps, standing erect and bending with no pain or discomfort.

Case 3—L. A., age 45; female—Polyarthritis

HISTORY

Onset of arthritis 1 year ago. Unable to walk for last 7 months. Onset in fingers and then knees. Left 2nd finger swollen, also both legs. Patient also had some pains in sacro-iliac region. Tonsillectomy performed but there was no relief of pain.

TREATMENT AND RESULTS

Patient received daily treatment because of limited stay in city for 2 weeks. After 1st week of treatment patient was walking better, using cane only for curbs, etc. After 2nd week's treatment cane was discarded. Able to climb steps, bend, etc. with little difficulty. Swelling of knees slowly receding. Walking well.

Case 4—O. B., age 44; female—Polyarthritis ——

HISTORY

Arthritis in both hands and wrists, stiffness of neck and shoulders. Had rheumatism in childhood. Tonsillectomy done several years ago with some improvement. Both hands and wrists show marked deformity. Severe pain in arms and in back of neck. Has had to discontinue her work as seamstress because of inability to sew or to hold needle. Unable to raise arms to horizontal level.

TREATMENT AND RESULTS

Given 1 ganglion treatment every other day for 5 days. At that time patient stated there was an improvement in sleep since she had formerly dreamed a lot and was a restless sleeper. Swelling of joints diminished; pain in neck gone. Marked increase of motion in both hands, joints and arms. Given 1 ganglion treatment every other week for 5 weeks. During this period patient returned to work. At present she is able to sew and use her hands without pain or any recurrence of pain. Swelling and deformity of wrists and knuckles almost gone. Patient does not need treatment but does come to report on her general health. She is feeling better than at any time she can remember in past 6 months and has gained 22 pounds.

Case Number Seven

Before Treatment



After Treatment



Case 5—Z. W., age 67; female—Polyarthritis

HISTORY

Has had arthritis in knees for past 6 months. Severe pain when walking or bending knees. In going up steps, takes one at a time. After sitting any length of time finds it hard to walk. Sleeps poorly. Walking with cane for support.

TREATMENT AND RESULTS

After 1st ganglion treatment patient was able to go up steps easily. Has pain when bending knees and walking. 1 ganglion treatment given every other day for 4 treatments, then 1 each week for 4 weeks. During this series patient was walking without cane. States she does most of her own housework and does not tire easily. Sleeping throughout the night. Patient has not been in for treatment for nearly a year but continues to report by phone of her doing all housework, feeling well and of gaining weight.

Case 6—F. G., age 49; female—Polyarthritis

HISTORY

Pain and stiffness in knees for past 15 years. At present unable to bend knees. Knees entirely stiff, swollen and painful. Unable to walk up and down stairs. Throws leg to one side when walking. Tires easily and sleeps poorly. No headache or sore throat. Several years ago had knees stretched and attempt to bend under general anesthesia.

TREATMENT AND RESULTS

After 1 ganglion treatment, patient was able to bend knees slightly. Received 1 ganglion treatment the following day which resulted in marked improvement. Patient now goes up and down stairs with less difficulty and pain. Walking seems to be more normal and she bends knees when walking. Patient received 1 ganglion treatment every day for 2 days, then every 3rd day for 3 treatments, then 1 application a week. States she is able to walk several blocks without tiring. Able to bend knees more after each treatment. Now doing most of her own housework. General condition greatly improved. She is less tired and is sleeping well. Calcium and Ironyl injections given with each treatment.

Case 7—M. G., age 51; female—Polyarthritis

HISTORY

Following a cold 2 years ago patient had onset of stiffness, soreness and swelling of all body joints. Swelling gradually subsided leaving arms stiff with inability to raise them to comb her hair or dress. Hips became very stiff so that patient walked with cane and was unable to go up more than 1 step at a time. Gold injections were given. Relief or swelling and stiffness of hands resulted but no improvements in hips. 6 months later given gold injection again but not effective. At this time patient was walking on crutches and unable to go up steps without difficulty and severe pain. Standing for any length of time causes severe pain. Also pain awakens her while sleeping.

TREATMENT AND RESULTS

Patient given 1 treatment daily for 3 consecutive days After the 1st treatment patient able to walk without crutches. Then seen for 3 consecutive days each week for 3 weeks. During 2nd week of treatment patient using cane only. Able to walk up and down steps with less discomfort. As the patient came from out-of-town she was seen for 3 consecutive days once a month for 3 months. During this time patient used cane only for suport and is able to walk several blocks without tiring. At present she is able to do all of her housework and has discarded crutch entirely. On 1 visit the patient came to the office from the station without using cane and carried a valise blocks without becoming tired. Each treatment was supplemented by calcium and Ironyl injections intramuscularly. Patient now returns for 3 consecutive treatments every 3 month. At last visit she came to office by bus. This was the 1st time she had been able to get on a bus for many years. She also reports wearing high heels, lecturing at Women's Club and dancing. X-ray of hips on 11-13-47 revealed articular spaces to be markedly narrowed. Acetabula shows increased density of bone. The heads of the femurs show rounded, cyst-like areas in particular on the right side. There are no marginal spurs. The pelvic bones show a decreased calcium content. Findings suggest an arthritic process of infectious origin.

Case 8—F. T., age 39; female—Polyarthritis

HISTORY

Arthritic pains in hands and feet. Swelling of hands and feet. Difficulty in walking. Swelling of joints of fingers. 7 years ago patient was "crippled up" and bedridden. Had tonsils and several teeth extracted with some relief. Sleeping poorly.

TREATMENT AND RESULTS

With 1 ganglion treatment patient able to walk about without pain. Given 6 treatments for 6 consecutive days. After each treatment pain became less and she was able to move more easily. Sleeping improved. Then given 1 treatment every other day for 3 weeks and then 1 each week for 3 weeks following which she was discharged. At this time swelling is entirely gone from the joints of fingers. No return of pain.

Case 9—W. A., age 49; male—Cervical arthritis

HISTORY

Arthritis in neck, shoulders and back for last 10 years. Pain almost continuous and at present more pronounced in left shoulder. No nasal discharge, sore throat or ear complaint. Sleeps poorly.

TREATMENT AND RESULTS

Patient given 1 application with immediate relief. Able to move neck without pain for first time in several years. Then given treatment every 4th day for 4 treatments. At the end of this time patient able to move neck and shoulder and to bend without pain. Sleeping through entire night. Patient now receives treatment 1 every 2-3 months and is continuing his work as construction engineer. As his work requires him to look upward a great deal, he has had no return of the original complaint.

Case 10—C. G., age 62; male Polyarthritis

HISTORY

Pains in both shoulders and wrists for past year. hands and fingers swollen. No swelling in shoulders. Swelling more pronounced in morning and it takes some time before it subsides. During this time hands perspire profusely. No headache, or nasal discharge. No operations. Sleeps poorly.

TREATMENT AND RESULTS

On first visit patient's hands and fingers were swollen. After the ganglion treatment swelling could be seen receding. He was also able to move his shoulders without pain, also fingers and wrists. Returned for treatment every day for 5 consecutive days. During this time he was able to move his arms over his head. He had no discomfort and states he has no swelling of hands and fingers. Patient then received 1 ganglion application every other day for 3 treatments, then 1 treatment each week for 2 weeks, then 1 each month for 2 months. He was discharged after this visit. At this time he is able to move shoulders, arms, hands and fingers. No discomfort or swelling. Sleeping very well and gaining weight. Calcium and Ironyl injections given with each treatment Patient has not returned to office for approximately 1 year. He is now living in Florida. Previously he had to give up his business because of the arthritic condition.

Case 11—H. E., age 34; male—Polyarthritis

HISTORY

Arthritis since 1944. Swelling of knuckles and fingers or hands, also swelling of feet. Pain when moving shoulders, more severe in the morning. Sore throat before onset of arthritis. No nasal discharge. Unable to close his hands or walk without severe pain. Received hot paraffin treatment while hospitalized by Army, in several different Army hospitals.

TREATMENT AND RESULTS

Patient received 1 ganglion application each day for 3 consecutive days. Immediately after each treatment the swelling of joints subsided and patient was able to walk and use hands and move fingers with very little discomfort. He then received 1 ganglion treatment 3 times weekly for 3 weeks. During this period swelling entirely relieved and he was able to use his hands and walk normally. Patient then returned to his position as salesman doing full-time service. One year following his discharge patient returned to office with an acute swelling of the left wrist but with no return of any swelling for which he was treated previously. Immediately after ganglion treatment the swelling subsided and the patient was able to use his hand with no pain resulting in the wrist. Patient returned for 2 days following for treatment. Each day there was no evidence of swelling and no pain in the wrist when using his hand. Patient now continuing his work as salesman which requires a great deal of walking. Has gained weight and is feeling fine. Treatments discontinued 6 months ago. Also discharged by V. A.

Case Number Fifteen

Before Treatment



After Treatment



Case 12—L. F., age 55; male—Polyarthritis

HISTORY

Arthritis since last May with pain and swelling of wrists, knees and ankles and pain in shoulders. Has difficulty in walking and wears shoes many times too large. No headache, nasal discharge or sore throat. No ear complaint.

TREATMENT AND RESULTS

Patient received 1 ganglion treatment each day for 3 consecutive days, then 1 treatment twice weekly for 2 weeks and then 1 treatment each week. Patient receiving treatments at this time. During this course of treatment patient appeared to be walking better. The hands are still swollen but swelling is less than when first treated and he is able to use his fingers which he was unable to do before starting treatment. Patient also states he is able to sleep much better and his appetite is greatly improved. Also, able to wear his shoes which he was unable to do before. 6 months ago patient travelled to the coast alone, changing trains and not being tired when arriving at his destination.

Case 13—S. O., age 47; female—Polyarthritis

HISTORY

Numbness in right hand. Stiffness in both shoulders and cramps in both thighs. No headache. Pains in shoulders worse in past few days. Severe cramps in legs. No nasal discharge. Hands show swelling of knuckles and wrists.

TREATMENT AND RESULTS

After 1st ganglion treatment numbness in hand, pain in shoulders relieved. Given ganglion treatment every 3rd day for 2 weeks. After this series of treatment patient showed definite improvement in hands, arms, legs and back. Continued treatment 1 every week for 4 weeks. No return of pain in that length of time. Marked increase in mobility of hands and arms with regression of swelling. Patient works in bakery and now is able to wrap packages with no discomfort in moving her arms or shoulders. X-ray of left shoulder: No fracture or dislocation. The humeral head is in normal relation with the glenoid cavity. Chronic hypertrophic osteoarthritis of the shoulder joint and of the acromioclavicular articulation. Large area of calcification within the sub-deltoid bursae.

Case 14—F. P., age 36; female—Polyarthritis

HISTORY

Pains and aches all over body. Pains in joints with swelling of hands, wrists and knees. Most severe pain and swelling of knees causes walking to be difficult and very painful. Unable to close hands. Some occipital headache. No vertigo, nasal discharge or sore throat.

TREATMENT AND RESULTS

After 1st ganglion treatment patient was able to close hands easily with no discomfort. Able to go up steps with ease. Given 1 ganglion treatment every day for 3 days, then 1 every 4 days twice. After this series there appeared a noticeable regression of swelling of joints. Patient now able to travel, climb steps with no discomfort whatsoever. Patient now receiving 1 treatment each month.

Case Number Sixteen

Before Treatment



After Treatment



Case 15—A. K., age 59; male—Polyarthritis

HISTORY

Arthritic deformities of hands, knees and elbows. Severe pain since 1932. Has been hospitalized but with no relief. Tonsillectomy in 1938. Received gold treatment for months but discontinued because of rash and no relief. Removal of bursa in left elbow in 1934. Has had several coronary angina attacks. Now has attacks on exertion and uses nitroglycerin. Has had x-ray therapy. Pain at present severe so that he takes 10-12 aspirin or anacin daily for relief. Walking with cane, needs assistance for steps. When sitting for any length of time, needs help to get up and has to stand several minutes before pain subsides to allow him to walk.

TREATMENT AND RESULTS

Patient given 1 ganglion treatment every other day for 5 treatments, then 1 every week for 5 treatments. At this time patient was walking much better and able to get up easily from a chair. Able to climb steps with little difficulty. Also able to hold a cup; before could hold glass only and that with difficulty. Continued treatments 1 every week for 2 weeks, then 1 every month. At present patient able to travel alone, feeds himself, buttons his own clothing and travels by bus to and from the office. There is also a noticeable lessening or swelling of the hands and feet. Now able to see joints of fingers.

Case 16—M. R., age 39; male—Marie-Strumpell Disease

HISTORY

Onset about 20 years ago. Began in sacro-iliac region, progressing to middle of back, neck and shoulders. Unable to straighten arms over head or have them meet at the back. Unable to rotate neck or move head, has to turn entire body to see. Can bend forward about 30° only. No history of sinus trouble, postnasal discharge, sore throat or ear complaint. Underwent a sacro-iliac operation several years ago but received no benefit from it.

TREATMENT AND RESULTS

Received 1 ganglion treatment each day for 6 consecutive days and at the end of this series patient was able to bend forward, nearly able to touch his knees and able to place his hands behind his back. Treatment continued every other day for 10 days (5 treatments). This series showed a marked improvement in the neck. Now patient was able to move his head slightly from side to side and up and down. Also able to touch the floor with his fingers. Back also improving and patient standing more erect. 1 treatment was given each week for three weeks, then 1 each month for 5 months. Examination of patient each month showed him able to move his head more and without difficulty. Patient states of his being able to run up stairs now, which was impossible before. Gaining weight and sleeping throughout the entire night. Previously he awakened to turn. These treatments were supplemented by calcium and Ironyl injctions intramuscularly;also by patient doing routine exercises each day.

Case 17—I. K., age 63;female—Polyarthritis

HISTORY

27 years ago patient had severe toxic thyroid. Was treated with cold packs. After this she developed arthritis in hands and shoulders. Unable to raise her shoulders. Hands are also deformed. Has had headaches lately. Sleeps poorly.

TREATMENT AND RESULTS

Received 1 ganglion treatment every 3rd day for 4 treatments. After this series patient was able to raise her arms above her head and move her fingers slightly. Then received ganglion treatment every week for 5 weeks. Patient now able to comb her own hair, button her clothing and to hold a cup without difficulty. Now receiving treatment monthly. Patient boasts of doing her own housework which she was unable to do before. She is also able to move and use her fingers and can now sew and do her mending.

Case 18—B. D., age 43; female—Polyarthritis

HISTORY

Arthritic pains, swelling of hands, wrists, neck, ankles and back. Unable to raise her arms. Duration 4 years. Arithritic onset occurred after typhoid injection in 1943. Occasional pain in left side of face. Occasional postnasal discharge. Has had some bladder disturbance.

TREATMENT AND RESULTS

Patient received 1 ganglion treatment every day for 3 consecutive days, then 1 treatment every 2nd day for 4 treatments. After this period patient is walking with more ease and less pain and discomfort. Swelling of hands subsided. Sleeping greatly improved. She also reports definite bladder improvement. She is now receiving 1 treatment twice a week. X-ray of right hand reveals atrophic arthritis with generalized bone decalcification and diminution of the interphalangeal joint spaces. Similar x-ray findings noted on the left with a free arthritic calcified deposit seen along the outer aspect of the 5th metacarpophalangeal articulation.

Case 19—R. E., age 71; female—Polyarthritis

HISTORY

Arthritis in hands, spine, neck and shoulders. Unable to move her shoulders or put her hands behind her back. Onset in knees about 1 year ago. Has had 24 gold injections with no relief. Has also had previous attack of arthritis about 19 years ago. Hospitalized for 5 months. After release from hospital walked on crutches and finally with cane.

TREATMENT AND RESULTS

Patient given 1 ganglion treatment with immediate relief. Then given 1 application every week for 6 weeks. During this time patient was able to rotate her shoulders, raise them above her head, tie her own apron and comb her hair. Patient continued on 1 treatment every 2 weeks for 3 treatments. She is now receiving 1 treatment every 4-6 weeks.

Case 20—E. Z., age 45; female—Polyarthritis

HISTORY

Has had arthritis of hands and feet for past 11 years. Also has pain in her back and neck; "practically in every joint of my body." Had typhoid treatment 8-9 years ago. Some nasal discharge. No headache. Slight sore throat at times. No ear complaint. Sleeps poorly because of pain. Pain worse when bending and walking down steps.

TREATMENT AND RESULTS

After the 1st treament patient received immediate relief and was able to go up steps with no discomfort. She then received 1 treatment every day for 4 consecutive days. Patient is now able to walk and bend with ease. Sleeping greatly improved. At present patient is under treatment.

Case 21—R. G., age 29; female—Polyarthritis

HISTORY

Arthritis of all joints, swelling of knees and ankles. Some swelling of hands and wrists. Tires easily. No headache. Some nasal discharge with occasional sore throat. No ear complaint. Onset of arthritis after childbirth.

TREATMENT AND RESULTS

1 ganglion treatment every day for 4 consecutive days. After this series patient was able to walk up steps with no difficulty. Swelling subsided in hands. able to see joints of fingers. Sleeping improved. 1 week later patient returned for 3 treatments in 3 consecutive days. During this week patient reported being able to walk along the country road of her home, being able to hold her baby which she had not done since its birth. Patient is under treatment at present. X-ray of the hands and ankles show atrophic arthritis with bone decalcification.

Case 22—F. G., age 75; female—Polyarthritis

HISTORY

Pain in left leg. Had neuritis 4 years ago which has recurred. Pain is mostly in left leg and thigh and seems worse when lying down and on turning in bed. Nose is dry. Both knees swollen and painful.

TREATMENT AND RESULTS

After 1 ganglion treatment patient received immediate relief. Received 1 ganglion treatment every 3rd day for a period of 2 months. After this period patient walking with very little pain or difficulty, climbing steps and doing her own housework and cooking.

Case 23 B. K., age 59; male—Cervical arthritis

HISTORY

Stiffness of back and neck for the last 2-3 years. Pain on motion. Pain when bending. No headaches, vertigo or postnasal discharge. Occasional pain in right chest. Was told he had calcium deposits in spine.

TREATMENT AND RESULTS

Given 1 ganglion treatment every other day for 3 treatments, then 3 times weekly for 3 weeks. After this series patient was able to rotate his head and use his neck and back muscles more than previously. Now receiving 1 treatment every week. At this time he is able to turn his head without difficulty instead of turning his entire body as previously. Patient also reports improvement in sleeping, not awaking to turn as he did before the treatment.

Case 24—C. V., age 24; female—Pelvic obliquity polyarthritis

HISTORY

In 1909 patient had severe painful cramp in right hip. Hospitalized for 6 weeks; leg shrank and shortened. At present she is suffering a great deal of pain in the right hip with extreme limitation of motion of right leg. Duration of present condition 4 years. Had some infection of right hip. Radical arthrotomy performed.

TREATMENT AND RESULTS

1 ganglion treatment for 3 consecutive days. Immediate relief with 1st treatment. Then give 1 ganglion treatment every other day for 3 treatments. Walking greatly improved and she could go up stairs easily. Then received 1 ganglion treatment each week for 5 weeks with definite improvement in patient's ability to continue her housework. Not tiring as easily as before. She is now employed, doing practical nursing.

Case 25—Dr. H. T., age 48; male—Cervical arthritis

HISTORY

Has had spasms of neck and shoulder muscles for past 15 years. Had Paget's of pelvic bones and femur. Occipital headaches radiating to frontal region. Slight nasal discharge. No sore throat or ear complaint. Gets tingling sensation in extremities during the night.

TREATMENT AND RESULTS

1 ganglion treatment every day for 5 consecutive days, then 1 treatment each week for 3 weeks. Following treatments patient was able to move his head, shoulders with no difficulty and has had no headaches since the 1st treatment. Also able to move his head without rotating body. Patient discharged after the 8th treatment.

Case Number Twenty-six

Before Treatment



After Treatment



Case 26—W. O., age 29; male—Marie Strumpell Disease

HISTORY

Able to stand alone but unable to bend. Onset of pain in right hip 5 years ago. Patient unable to stand any pressure on right leg, resorted to crutches. On crutches for 3 months. Hospitalized 14 months. Given physiotherapy and injections of rheumatoid vaccine. Walked with crutches for 3 months following discharge from hospital. Admitted to hospital again and unable to walk in hospital for 5 months. Used wheel chair. After discharge was admitted to hospital in Pa. for plastic acetabulum operation on right hip. Legs became straight. Hospitalized for 4 months. At that time he was only able to stand or lie down, being unable to sit or move hip even slightly. Walking with crutches and is only able to walk about 2 blocks before becoming ill and having to lie down. Eats lying down. Tiring very easily. Patient had scarlet fever at age 15.

TREATMENT AND RESULTS

Patient came to office 3 times weekly for treatment for 3 months, then 1 treatment each week for 6 weeks. After this patient was able to walk without crutches and was able to move his head up and down and rotate it. Now able to dress himself and is walking with crutches outside only for aid with curbs. Also is able to climb steps twice daily to 3rd Avenue Elevator. General condition greatly improved. Sleep also improved.

Case 27—L. L., age 53; male—Cervical arthritis

HISTORY

Stiffness of neck for last 8-10 years. X-rays show advanced osteoarthritis. Bending the head back is very difficult and painful. Unable to rotate head. Position of body and head rigid and forward.

TREATMENT AND RESULTS

Patient given 1 ganglion treatment every day for 3 days, then 1 treatment 3 times weekly for 3 weeks. After this series patient was able to stand more erect and bend the head back. Then received 1 treatment every week for 4 weeks. Now able to bend head forward and rotate from side to side, with little discomfort. Able to sleep better at night. Patient now under treatment.

Case 28—F. M., age 65; female—Polyarthritis

HISTORY

Pains in arms, hips and knees. Onset about 15-18 years ago. Swelling of left wrist and hand. Pain on elevation of left arm. Pains in knees when sitting for any length of time. Tonsillectomy 30 years ago.

TREATMENT AND RESULTS

Given 1 ganglion treatment every other day for 5 treatments, then 1 ganglion application every 10 days for 3 treatments. Patient then discharged. After 5 treatments patient showed improvement and at the time of discharge she was able to raise her arm with no difficulty. Swelling of wrist and hand greatly diminished. After traveling by bus and sitting for over 3 hours patient reported no pain or discomfort in the knees when the ride is over.

Casee 29—A. K., age 41; female—Polyarthritis

HISTORY

Pains in back, hands, knees and elbows for last year. Pain when bending and going up steps. Injured cartilage of right knee 2 years ago, preceding present complaint. No headache, nasal discharge or sore throat. Tonsillectomy performed at 6 years of age.

TREATMENT AND RESULTS

Given 1 ganglion treatment weekly for 6 weeks. After this series patient was able to bend and climb steps more easily and with less pain. No pain in hands or elbows. Now coming for treatment once monthly. Patient travels from Philadelphia and brings her small child with her. Travels from station by bus and complains of no pain or discomfort after the trip.

Case 30—R. G., age 61; female—Polyarthritis

HISTORY

Since last summer patient has had severe pains in shoulders. Unable to move her shoulders. Now has pains all over her body. Hands and knees are swollen. Pains on walking, particularly on steps. Sleeps very poor because of pain.

TREATMENT AND RESULTS

After 3 consecutive ganglion treatments patient showed marked improvement. Able to move shoulders without pain and has less pain when walking. Then received treatment every 3rd day. Treatments then given one weekly for 2 weeks. Patient is under treatment at present, once a month. Now able to move her shoulders easily and comes to the office by subway. No difficulty with steps or walking. Sleeps through the entire night.

All of the patients received in addition to the sphenopalatine ganglion treatment tri-weekly injections of Ironyl mixed with injectable B-complex intramuscularly as well as injections of Calscorbate. They were given one tablespoonful of Co-amino three times daily in cold water and 6 tablets daily of Ferro-C.

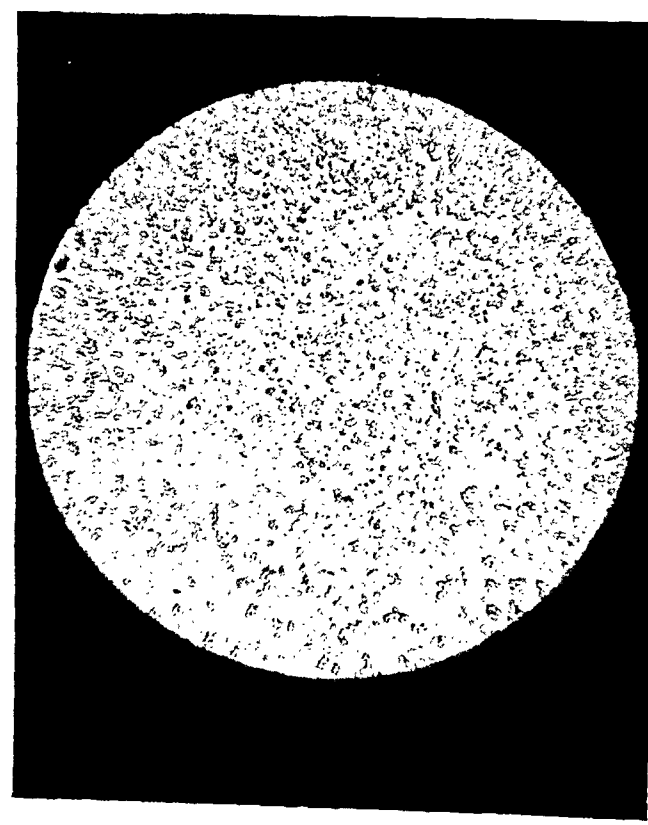
The Rh Pseudoagglutinative Properties Of Porcine Parotid Mucin

By
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HERBERT A. WEITZNER**
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WE have recently described the preparation of a fraction from hog gastric mucin which agglutinated suspensions of human Rho positive erythrocytes.[1] Many commercial therapeutic mucin preparations are fortified with hog salivary gland mucin.[2] We had accidently discovered an Rh agglutinin in the latter before its demonstration in gastric mucin though we had been on the look-out of such antibodies in mucin-containing products in general.

During the administration of IV-6 human plasma fraction intravenously to human subjects, [3] we encountered an occasional systemic reaction similar to that following incompatible blood transfusion.

FIGURE I



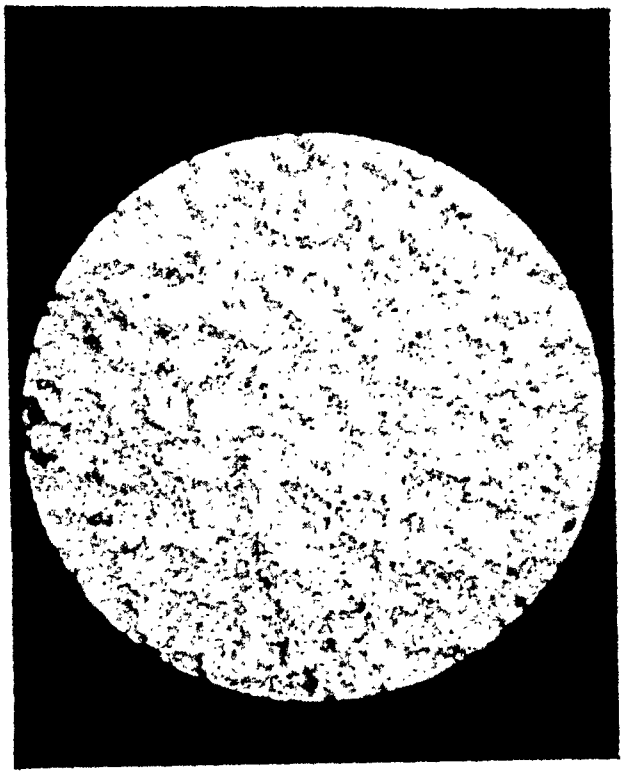
Rouleaux formation by Rh positive erythrocytes in 7% porcine parotid fraction in physiological saline immediately after admixture.

*The investigation reported herein was carried out during 1946 and 1947 at Halloran General Hospital, Staten Island, N. Y. and the Batavia (N. Y.) VA Hospital. The authors are indebted to J. W. Mentha, formerly Chemist, War Department, Halloran General Hospital, for various chemical fractionations, to Dr. Edward Campbell of the Lilly Research Laboratories and to Drs. J. B. Lesh and Jules Porsche of Armour and Company for porcine parotid products.

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FIGURE II



Beginning pseudoagglutination by agglomeration of rouleaux. A transition stage between Figure I and Figure III.

Analysis of the incidence of the reactions showed them to occur in Rh positive individuals. One Rh negative subject who received an infusion of IV-6 fraction (as a source of cholinesterase) subsequently exhibited Rh "blocking" antibody though this subject had never previously been transfused. It was found that IV-6 human plasma fraction contained such "blocking" antibodies or pseudoagglutinins.[4] Their association with the glycoprotein-mucoprotein component of IV-6 suggested that Rh pseudoagglutination might be a property of mucinous proteins in general.

The mucin-containing fraction IV of porcine parotid (which had been prepared as a potential therapeutic cholinesterase source[5]), showed similar Rh antibodies. The Rh agglutinating potency of parotid mucin fraction is not, however, contingent on cholinesterase content since the former persists after complete inactivation of the latter. Because of the relative chemical homogeneity of porcine as compared to gastric mucin, it was believed that a more definitive study of the mechanism of its Rh agglutinative effect could be conducted with the salivary gland extract. Its preparation and properties are therefore described and their bearing on certain problems connected with Rh pseudoagglutination is discussed.

Actively agglutinating fractions have also been prepared, by alcohol and by ammonium sulfate precipitation. Rh agglutinins, like the cholinesterases, are found in a rather wide "spectrum" of fractions. By ammonium sulfate precipitation, between 50 and 66% saturation of the starting extract, we have contained a cholinesterase containing product assaying 4000 Alles and Hawes,[6] units/gram. This material, on intravenous injection into rabbits, causes a sustained rise in the blood cholinesterase content without apparent toxicity but its use in humans has not been attempted because of the associated human erythrocyte agglutinin. While hog gastric mucin is reputedly toxic when given parenterally to animals,[7] the parotid mucin seemed to be devoid of such effects in the rabbits used.

Preparation of Hog Parotid Mucoprotein

One kg. of fresh hog parotid from which gross fat and lymphoid tissue had been trimmed, was frozen, pulverized and ice dried. The comminuted fat was removed by four washings with petroleum ether. The dried fibrous residue was extracted with three volumes of distilled water with periodic agitation for twelve hours. The extract was filtered through cotton and the filtrate retained.

Sufficient twenty percent acetic acid was added to the filtrate to bring the pH to 4.5. The flocculent material which separated was removed by centrifugation. To the supernatent, sufficient NaCl was added to bring the ionic strength to 4.0. The salted out protein was recovered by centrifugation and dried. The recovery from 1 kg. of fresh gland is about 15 grams of concentrate. This fraction was used for the Rh pseudoagglutination studies*.

FIGURE III

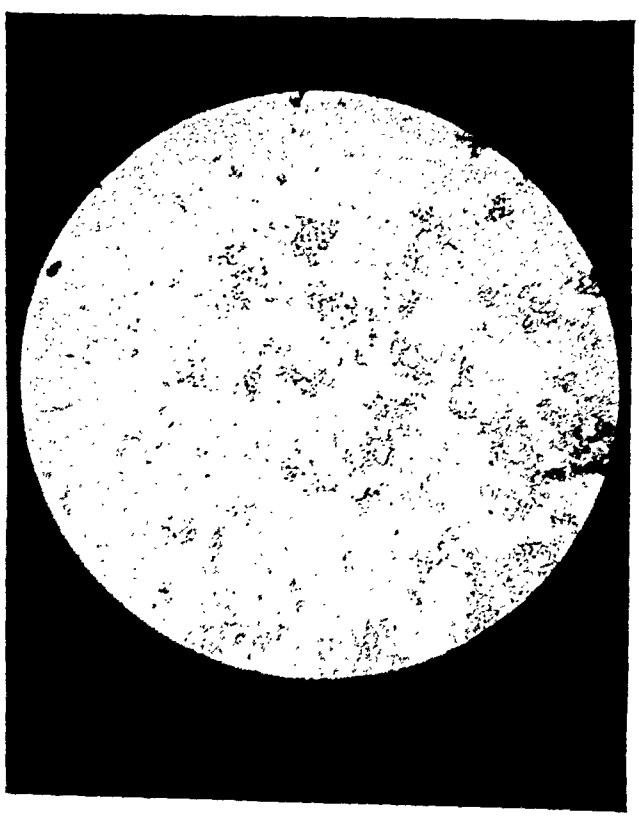


Complete pseudoagglutination by combination of most rouleaux in the field. This picture is macroscopically indistinguishable from specific hemagglutination but the rouleaux characteristics can still be seen by microscopic examination of the individual agglomerates. This type of pseudoagglutination is produced by the "slide test" Rh antiserums.

Rh Testing Against Human Erythrocyte Suspensions

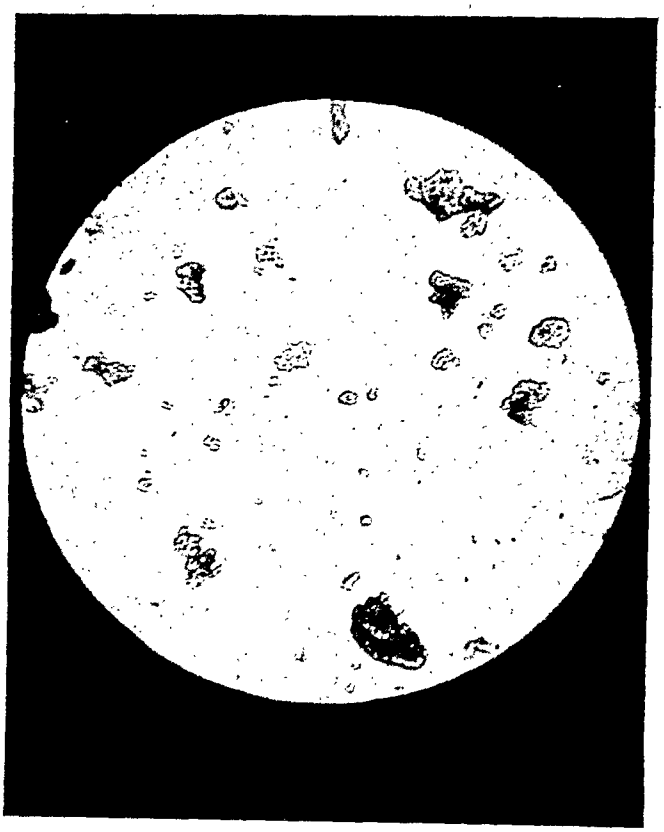
(A) Slide Testing. This is essentially the test advocated by Diamond for the conjoint demonstration of "agglutinating" and "blocking" antibody.[8] A drop of oxalated or citrated[9] whole blood was mixed on a well-slide with a drop of solution of porcine parotid extract. Various preparations of the latter in saline, bovine albumin or modified human globin[10] solution were used. (Modified human globin was found to be thromboplastic when used with citrated blood suspension and its use as a diluent was therefore abandoned). Agglutination was read on a frosted glass illuminator after an arbitrarily selected interval of 5 minutes. All readings were checked microscopically. The optimal concentration of porcine parotid extract that would agglutinate Rho positive, and fail to agglutinate Rh negative erythrocytes (as designated by the use of a "standard" slide-test serum), was found to be 3.5% in physiologic saline. A 7% solution, while increasing the degree of agglutination, tended to introduce confusing rouleaux whereas similar confusion resulted from either globin or albumin fortification; the latter appeared

FIGURE IV



Pseudoagglutination in dilute porcine parotid extracts, unfortified by albumin, gelatin or globin. There is no tendency toward rouleaux and the cells adhere by their edges to form bidimensional aggregates. A similar picture is seen in sludged cells, whether from p. falciparum infection or severe atypical pneumonia. It can also be produced by any lipolytic hemolysin in small dilution or by scarlet runner bean extract.

FIGURE V



Fibrinous pseudoagglutination of erythrocytes by globin. Rouleaux first form due to the high viscosity of the globin solution which then exerts a thromboplastic effect, precipitating a coating of fibrin which mats together individual rouleaux. A similar type of fibrinous agglutination is occasionally encountered while attempting cross-matching of blood from dicumerolized subjects.

to increase the avidity[11] of the parotid material toward Rh positive erythrocytes without affecting the specificity of the reaction.

(B) Tube Testing. This was conducted by the method of Wiener and Landsteiner.[12] The agglutinating titer of the dried parotid fraction, based on the minimum concentration in saline necessary to give demonstrable agglutination of a 2% washed erythrocyte suspension, varied with the batch of cells used, from 1:64 to 1:1024.

(C) Blocking Antibody Testing. The method described by Potter[13] was used. Because of the high manifest agglutinative titer of the material, "blocking" effect was not directly elicited.

RESULTS

(A) Slide Test. Of 300 samples of blood tested, 265 were positive by IV-6 plasma fraction and 249 by the test with porcine material. With the latter, the degree of agglutination in positive instances was in all cases less than that produced by human antiserum; it was, however, macroscopically and microscopically definite. As shown in Table I, the 16 instances of discordancy were in all but two instances, on the negative side with the porcine reagent. The degree of concordance be-

tween porcine and human anti Rh agglutinin in this series, with this test, is considered to be statistically significant. Since a reagent which gives a minimum of 80% positive results with Caucasian blood specimen is applicable as an Rh testing "antiserum," the use of porcine parotid mucoprotein as a screening reagent for Rh typing is under investigation.

(B) Tube Test. The results are given on a smaller series in Table II. Here the discordancy between human and porcine material was on the positive side for the latter but still with a correlation that can be considered statistically significant.

(C) Blocking Antibody Test. The evidence for blocking antibody effect of porcine parotid extract, in view of its direct agglutinative effect, is necessarily indirect. As in the case of human Rh blocking antibody reaction or "conglutination," agglutination is less pronounced, the older the blood specimen. This feature furnished the original correlation between porcine and human anti-Rh reagent typified by IV-6 plasma fraction. The latter has a directly demonstrable blocking antibody titer of 1:4 in 20% solution.*

One of the methods of eliciting blocking antibody action consists in the suspension of the Rh positive erythrocytes in menstruums of high protein concentration. This is usually done by fortification of the Rh antibody with gelatin, bovine albumin, fibrinogen or globin. Addition of any of these proteins to porcine parotid extract markedly increases the degree of demonstrable agglutination that the porcine material will produce. This is apparently due to acceleration of rouleaux formation by the increase in viscosity, or possibly the dielectric constant of the menstruum. Figures I, II and III show the transitional stages between simple rouleaux formation and Rh "agglutination" produced by protein fortified porcine parotid extract. Figure IV shows the type of agglutination produced by dilute (2%) porcine parotid in the absence of adventitious protein. Rouleaux are absent; the clumping is bidimensional and similar to that previously referred to as pseudoagglutination."

Modified human globin solution, by itself, produced a morphologically similar clumping of rouleaux of both Rh positive and Rh negative erythrocytes when these cells are suspended in citrated plasma. This has been shown to be due to the adhesiveness of the fibrin formed on the surface of such cells through the thromboplastic effect of globin (Fig V). While globin "pseudoagglutination" is merely a physical phenomenon that has no immunologic significance, its similarity to agglomerization of erythrocytes by Rh antiserum permits an explanation of the long-sensed difference that existed between that phenomenon and a truly specific immunologic phenomenon such as anti-A or anti-B hemagglutination.

*Dr. Philip Levine of the Ortho Research Foundation kindly furnished us with the results of the blocking antibody titer determination on IV-6 plasma fraction.

DISCUSSION

Barnard" in a study of the physical differences exhibited by various erythrocyte aggregates, concluded from the reversibility and the morphology of Rh positive erythrocyte clumping by anti-Rh reagent that the latter phenomenon was an example of pseudoagglutination rather than one of specific hemagglutination. Pseudoagglutination is now more familiar as the "sludging" that takes place intravascularly in such a condition as falciparum malaria infection where the parasitized cells become sticky and adhere passively by their edges. The morphology of such aggregates is well shown in Figure V. The area of contact between cells in the aggregate is small, cohesiveness is therefore not marked and the aggregates of either "sludged" blood or that of Rh pseudoagglutinated blood can be broken up by agitation. The tentative conclusion advanced at the time: that this was not specific hemagglutination seemed to be negated by the evolution of the slide test and the demonstration of blocking antibodies, for, in menstruums of high protein concentration the aggregates do appear as though they resembled active agglutination such as A or B hemagglutination.

Analysis of Figures I to III indicates that this resemblance is accidental and that high protein concentrations introduce an artifact into pseudoagglutination that accounts for the resemblance. In menstruums of high protein content, the passive cohesiveness of pseudoagglutinated erythrocytes is amplified by the coexisting tendency for rouleaux formation. There is greater area of surface contact between the apposed faces of the "sticky" cells in rouleaux than there is in cells with apposed circumferential surfaces. The rouleaux, themselves, composed of adhesive cells, have adhesive exteriors and several of them will adhere to similate specific hemagglutination aggregates. The aggregates do not dissociate on agitation because, as Kegerreis has shown" in highly viscous media, agitation serves to intensify rouleaux. There is probably no essential difference between Rh "blocking antibody" conglutination and Rh agglutination; they both seem to be instances of pseudoagglutination of the erythrocytes of a certain percentage of humans that can be effected by mucoproteins or mucins of non-human origin.

Whether intravascular sludging, which is also an instance of erythrocytic pseudoagglutination, is in any way connected with the mucoproteins of the plasma is a question that remains to be answered. A marked rise in the mucoprotein concentration of the blood in malignancy has recently been reported."

The demonstration of an "antibody" against certain human erythrocytes in tissues other than those of primates and particularly their autochthonous occurrence in such tissues, may be of interest to the phylogeneticist. Our concern is the possible reflection of the fact on clinico-pathologic and medico-legal practice. Whether porcine parotid fraction will afford a dependable, less expensive reagent than human material remains to be determined.

TABLE I

Comparative Slide Test Reactions with Porcine Parotid and Human Anti-Rh Reagent In 300 Blood Samples

Reagent	I IV-6 Plasma Fraction	II Porcine Parotid	III "Standard"*
Number Rh positive	265	249	255**
Percent Rh positive	88.3	83.0	85.0**
Number Rh negative	35	51	45**
Percent Rh negative	11.7	17.0	15.0**
Positive I; Negative II		18	
Positive II; Negative I	2		
Negative II; Positive III			9***
Negative III; Positive II		2***	

*"Conglutination" anti-Rho serum, Certified Blood Donor Service, Jamaica, L. I., N. Y.
**Figures furnished by distributor
***Comparisons made only with discordancies between I and II.

TABLE II

Comparative Tube Test Reactions with Porcine Parotid and Standard Human Anti-Rh Serum in 100 Blood Samples.

Reagent	II Porcine Parotid	IV Rh "agglutinating" Antiserum*
Rho positive	88	74
Rho negative	12	26
Positive II; Negative IV	16	
Positive IV; Negative II		2

*Tube Test anti-Rho serum, Certified Blood Donor Service, Jamaica, L. I., N. Y.

SUMMARY

The preparation of a porcine parotid mucoprotein fraction which selectively agglutinates human Rh positive erythrocytes, is described. Solutions of the extract parallel the effect of antiserums of human sources.

From a morphologic study of the effect on Rh positive erythrocytes, of porcine parotid extract in various protein menstruums, it is concluded that there is no essential differences between Rh blocking antibody effect and Rh clumping, both being instances of pseudoagglutination.

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Clinical And Roentgenologic Aspects Of Esophageal Lesions In Scleroderma

REPORT OF SIX CASES*

By

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THE appearance of the skin in scleroderma is so striking that the visceral manifestations of the disease often go unnoticed. As early as 1897, Hektoen[1] described atrophy of the thyroid gland with endarteritis, and hyperchromatophilia of the pituitary in a case of scleroderma. Matsui[2] in 1924, on the basis of six carefully studied cases, showed that generalized scleroderma is a systemic disease in which all the viscera are involved. Rake[3] in 1931 described the clinical and pathological findings in a patient who 8 years previously had suffered from "attacks that suggested spasm of the eso-

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phagus" and in whom contraction of the lower end of the organ had been demonstrated roentgenologically. This was the first report of esophageal involvement demonstrated by roentgen examination. Six years later this same patient developed lesions in the stomach, small intestine and colon which were demonstrated on x-ray and confirmed subsequently at autopsy. Since this report many others have appeared. [1, 2, 3, 4, 5, 6]. Rafsky and Hertzig[7] recently described two cases, in one of which a biopsy specimen was obtained in the course of esophagoscopic examination.

The following cases are being reported to emphasize the occurrence of esophageal lesions in scleroderma, and to stress the clinical and roentgen findings.

REPORT OF CASES:

Case 1.—S. K., a 58-year old married white female was admitted to the hospital November 27, 1944.

She had been well until five years prior to entry when she noted tautness of the skin of the fingers, with pains in the joints. The fingers would turn white and blue on exposure to cold. With passage of time, her condition became worse and the skin of the face and legs became involved. She could not straighten her fingers, which were held in a semi-flexed position, and, within the last few months, she noted a stiffness of her ankles. For the last six months, she had had epigastric distress and heartburn unrelated to meals.

The past history, family history, and review of systems were non-contributory.

The physical examination revealed an elderly white female, with the characteristic facies of advanced scleroderma. The skin was thickened, hairless and taut. Over the fingers, which were semi-flexed, the skin was smooth and shiny. The skin on the forearms and ankles was thick and glossy. The eyes, ears and nose were negative. The mouth could be only partially opened, and the skin of the lips was indurated. The lungs were normal. On percussion the heart was enlarged to the left, and on auscultation an apical systolic murmur transmitted to the axilla was heard. The liver and spleen were not palpable. The blood pressure was 140 mm. systolic and 90 mm. diastolic.

The pertinent laboratory data were as follows:—The hemoglobin was 11.5 grams per 100 cc. of blood, and the erythrocytes numbered 4.3 million per cu. mm. The leucocytes totaled 11,500 per cu. mm. with normal differential count. The fasting blood sugar was 87 mg. and the blood urea nitrogen 13 mg. per 100 cc. The serum calcium was 10.6 mg. and serum phosphorus 3.5 mg. per 100 cc. The Wassermann and Kahn tests were negative and the electrocardiogram was within normal limits.

Roentgen examination of the gastrointestinal tract was negative except for the esophagus. The upper third of this organ showed slight widening, with normal peristalsis. The lower two-thirds was markedly dilated, with absence of longitudinal folds and peristaltic waves. The barium remained in the esophagus for many minutes before dropping into the stomach. The diaphragmatic portion of the viscus showed normal contraction and relaxation and the mucosal pattern was normal. There was no stenosis at the cardia and the dilated esophagus emptied in a normal manner. The cardiac sphincter was competent. A diagnosis of diffuse, generalized scleroderma with involvement of the esophagus was made.

Course in the hospital: The patient received diathermy and carbon dioxide baths and other symptomatic measures with some improvement. She was discharged from the hospital March 3, 1945, slightly improved.

Case 2.—T. D., a 31-year old married white female entered the hospital June 7, 1944, complaining of pain in the right eye; pains in the ribs radiating to the shoulders which were made worse by respiration, and epigastric discomfort. The family history was unimportant. Her present illness started 2 years previously when she noticed blanching of the fourth right finger on exposure to cold. Within two months, all the fingers of both hands were involved. The patient noted that emotional stress precipitated numbness, blanching, and cyanosis. In March 1944, the toes were involved in the same manner. One year prior to entry, the fingers became swollen, with tenseness of the skin, and pain in the phalangeal joints. At the same time, the shoulders began to ache, and she developed stiffness in movement of the lips. She had frequent bouts of low grade temperature. On two occasions, she was a patient at another institution where she was treated with dihydrotachysterol without improvement.

The physical examination showed a chronically ill woman with tan-tinged and shiny skin. There was a patchy pigmentation and depigmentation over the feet, legs, and upper chest, neck and forearms. The skin of the face was indurated and there was difficulty in moving the lips. The fingers showed a waxy cyanosis, and there was a marked atrophy of skin over the finger joints, with limitation of motion. There was some limitation of motion of the shoulder joints. The remainder of the physical examination was not remarkable. Laboratory data disclosed the blood urea nitrogen to be 7.5 mg., fasting glucose 86 mg., and uric acid 6.7 mg. per 100 cc. of blood. The serum calcium was 10.8 mg., the phosphorus 4.3 mg. and the chlorides were 368 mg. per 100 cc. The alkaline phosphatase was 3.8 Bodansky units. The carbon dioxide combining power was 60.5 volumes per cent. Urinalysis was normal. Examination of the blood showed a microcytic, hypochromic anemia—the erythrocytes numbering 3.79 million per cu. mm., and the hemoglobin 10.4 grams per 100 cc. The leucocyte count was 8450, with a normal differential. X-rays of the chest, skull, spine, tibia and fibula and the genito-urinary tract were negative. There was a small area of bone resorption in the head of the middle phalanx of the right middle finger. A diagnosis of generalized scleroderma was made.

The patient was given 2 grams of ferrous sulphate daily and carbon dioxide baths. With this regimen, she showed little improvement and was discharged September 17, 1944, slightly improved.

On re-admission October 12, 1944, the chief complaints were loss of weight and fever. She now had constant fever which reached a daily peak of 102° F. In December she developed a pericardial effusion with a temperature of 103° F. A pericardial tap revealed the effusion to be turbid, sterile on culture, and to contain 6.3 grams of protein per 100 cc. of fluid. Other laboratory findings were: Blood urea nitrogen 39.4 and creatinine 2.4 mg. per 100 cc. The plasma proteins totaled 7.3 grams with 3.4 grams of albumin and 3.9 grams of globulin per 100 cc. The carbon dioxide combining power was 45.3 volumes per cent. Repeated blood cultures were negative. The electrocardiogram showed inversion of T waves in all leads.

Anorexia, combined with difficulty in movement of the lips, and the prolonged fever lead to rapid deterioration and patient expired on January 8, 1945. The final diagnosis was diffuse scleroderma.

The necropsy revealed the following: There was fibrous thickening of the submucosa of the esophagus and cardia with ulcerative esophagitis. Microscopically, the esophagus showed many ulcers, extending into the submucosa. The bases of these ulcers consisted of the lamina propria which showed proliferation and engorgement of the capillaries and extensive infiltration of small round cells and few polymorphonuclear leucocytes. In more recent ulcers, the infiltration was predominantly polymorphonuclear in character. There was less marked diffuse infiltration of the entire propria beneath the intact mucosa, with plasma cells, lymphocytes and polymorphonuclear leucocytes, some of which were eosinophilic. There was considerable thickening of collagen bundles in the submucosa, especially in the section from the cardiac end. In this region, small arterioles and arteries show moderate hyperplastic thickening.

The mucosal lining of the stomach was desquamated. There was an excess of plasma cells and lymphocytes in the propria. The submucosa showed thickening of the collagen fibers similar to that seen in the esophagus. This change was especially noted in the sections from the cardia. In a section through the fundus, there was some vascular hyperplasia with necrotic changes in the wall of a venule, which was diffusely infiltrated with degenerating polymorphonuclear leucytes.

In the first portion of the duodenum there was an ulcer involving the mucosa and the entire submucosa. The submucosa around the ulcer was infiltrated with plasma cells, lymphocytes, polymorphonuclear leucocytes. On either side of the ulcer, there was a zone of fibrinoid necrosis beneath Brunner's glands.

Case 3.—E. S. a 35-year-old single white female entered the hospital July 28, 1943, complaining of epigastric pain and heartburn of several years' duration. Her present illness began fifteen years previously when she noticed blueness, coldness, and "pins an needles" sensations of the fingers, toes, ears, and nose. While always present in some degree, these symptoms became worse in cold weather. The stiffness of the fingers beame so marked. that it became necessary to warm her hands on the gas stove before being able to dress. In order to sleep in cold weather, she had to wear two pairs of woolen gloves and use a hot water bottle. Two years later she developed an ulcer on the distal phalanx of the right middle finger, which was refractory to all treatment and which led to an amputation of the part. This was followed by ulceration of all fingers. In 1934, she began to have arthralgia which starting in the fingers soon affected the spine, shoulders and elbows. Eventually, all the joints became involved. In 1935, she entered another institution where diagnoses of scleroderma, Raynaud's disease, and adenoma of the thyroid gland were made. She was subjected to partial thyroidectomy and parathyroidectomy, with temporary improvement. In 1937 she was re-admitted to the same hospital with a right thoracic sympathectomy and paravertebral block was done. In all, she was a patient in the same institution on seven different occasions and beside the above mentioned therapy she was treated with hyperthermia, mecholyl iontophoresis, and dihydrotachysterol.

In 1938, she developed a macular rash on the nose and face which has persisted to date. The lesions were circular, about one-half inch in diameter, and painless. At the same time, she began having difficulty in opening and closing of the eyes, and moving the lips. Concurrently, she began to have epigastric pain, with heartburn after meals which she described as constant "day and night." It was not influenced by diet but was made worse by fatty foods and coarse vegetables. The pain which at first was localized to the epigastrium later spread to involve the entire right upper quadrant.

In May 1943 she had an attack of excruciating pain, about forty-five minutes after supper which made her "double up." This started in the epigastrium, radiated to the umbilicus, and then to the right upper quadrant. The abdomen became distended and hard. These attacks occurred on three occasions and passed away spontaneously.

The physical examination revealed a moderately nourished young woman with a striking deficiency of lower eyelid lashes. There were erythematous, macular, telangiectatic areas over the cheeks, nose, and palmar surfaces of the hands. Ankylosis of the distal phalangeal joints was present. Most of the digits were ulcerated, and the nails were atrophic. The eyes, ears, nose, mouth were negative. The lungs were normal. The heart was enlarged to the left, the apex being felt in the sixth intercostal space in the anterior axillary line. The rhythm was regular, and there was a high-pitched systolic murmur over the mitral area, which was transmitted to the left axilla. A rumbling diastolic murmur was also heard in this area. Over the aortic area, there as a low-pitched systolic murmur. The second cound was muffled. There was a high-pitched systolic blow in the tricuspid area. The liver was palpable three fingers breadth below the costal margin. The spleen was not palpable. The toes, which bore the scars of previous ulcers, were well preserved. The neurological examination was negative.

Laboratory data:—Blood urea nitrogen was 19.1 mg. and glucose 86 mg. per 100 cc. The serum calcium was 10.6 mg. and phosphorus 3.9 mg. per 100 cc. Alkaline phosphatase was 4.7 Bodansky units, and urea clearance 43 cc. or 57 per cent of average normal. The red blood count was 3.8 million erythrocytes per cu. mm.; and the hemoglobin 10.5 grams per 100 cc. The leucocytes numbered 10,550 per cu.mm. with 67 per cent polymorphonuclears, 22 per cent lymphocytes, 5 per cent monocytes, and 6 per cent eosinophiles. The erythocryte sedimentation rate was 20 mm. per hour by the Wintrobe method. On gastric analysis there were found 80 units free and 98 units total acid. The stool was negative for occult blood and ova. The electrocardiogram showed low T1, T2 and a diaphastic T in CF2, indicating myocardial damage. The basal metabolic rate was plus 40.

X-ray examination of the chest demonstrated calcified densities in the clavicular regions which were probably lymph nodes. The heart was enlarged to the right and left and had the configuration frequently seen in mitral disease. Skeletal x-rays showed calcification in the region of the knee joints, and in the calves. A gastrointestinal series showed a dilated and elongated esophagus. The stomach and small intestine were normal. An examination by barium enema disclosed no abnormalities. On the basis of the clinical picture and associated findings, a diagnosis of diffuse scleroderma with esophageal involvement was made.

Course in the hospital: The patient was given dihydrotachysterol, beginning with 0.5 cc. and increasing the dose to 2 cc. per day. Diathermy was applied to the joints. The course was progressively downhill, and, after a severe nasal hemorrhage, she expired May 8, 1944.

Case 4.-R. S., a fifty-nine year old female, entered the hospital April 13, 1945, complaining of sacral decubitus ulcers of two months' duration. The family and past history were of no importance. The present illness began 12 years ago when the patient noticed that the fingers would turn blue on exposure to cold, and it became necssary for her to wear woolen gloves. At the same time, she noted an increasing stiffness of the hands, with hardening of the skin, especially on exposure to the sun. During the 18 months previous to hospital admission the stiffness had become marked and small ulcers appeared on the knuckles and the bony prominences of the fingers. In October 1944, the patient awoke one night to note that

there was no sensation in the fourth and fifth toes of the right foot. The next morning, the toes were swollen and bluish-purple. She was admitted to another institution where a mid-thigh amputation was performed. During the next year, she had many nose bleeds, and had noticed marked stiffness in the spine and left knee. She also complained of nausea but no vomiting had occurred. For th last month, she had been confined to bed because of the painful knee, and during this time she developed the bed sores for the treatment of which she entered the hospital. The patient had no complaints referable to the gastrointestinal tract.

Physical examination showed a chronically ill, elderly white female, well developed but poorly nourished. There was hyperpigmentation of the skin of the arms, most marked peripherally, with little areas of vitiligo at the pressure points. The skin of the face was atrophic, shiny and tense. The mouth could only be opened with difficulty. The fingers were stiff; the hands were held in the claw position. There was marked diminution of motion of the metacarpalphalangeal joints, the wrists and the elbows. The head and neck were negative. The heart was enlarged on percussion. The sounds were of poor quality. A systolic murmur was heard at the apex and P2 was louder than A2. There was a harsh murmur over the precordium, loudest in the third and fourth interspaces to the left of the sternum, which was transmitted to the right, and which was heard best at the beginning and end of systole. Blood pressure was 160 systolic and 74 diastolic. The apical rate which equalled the pulse rate was 132. The rhythm was regular. A smooth, non-tender liver edge was palpable two fingers below costal margin. The deep tendon reflexes were hypoactive. There were no pathological reflexes. The clinical impression was scleroderma with Raynaud's syndrome.

The laboratory examination disclosed the following: The blood urea nitrogen was 19.4 mg. and fasting glucose 83 mg. per 100 cc. of blood. The serum proteins were 7.3 gm., the albumin fraction being 3.9 gm. and the globulin 3.4 gm. per 100 cc. The total blood cholesterol was 192 and the esters 135. The cephalin flocculation test was negative. The urinalysis was essentially negative. The blood showed 8.9 mg. of hemoglobin; the erythrocytes numbered 3.2 million per cu. mm. and the leucocytes 18,400 per cu. mm. The differential count disclosed 92 per cent neutrophiles, 6 per cent small lymphocytes, and 2 per cent monocytes. The sedimentation rate was 31 mm. in one hour. The stool guaiac test gave a 4 plus reaction. The Wassermann and Kahn tests were negative. The electrocardiogram was normal except for low voltage.

On roentgen examination the entire esophagus was dilated and the walls were rigid. Peristalsis was present only in the lower third, and the cardia was normal.

The lungs showed diffuse pleural thickening in the infraclavicular and apical regions. The pulmonary markings were greatly increased. Both hila were elevated, and there were calcific deposits, probably representing lymph nodes, more marked on the right. The heart was negative. There were irregular areas of bone absorption involving the fifth, sixth, seventh ribs posteriorly. It was concluded that the thoracic and pulmonary changes were most likely due to diffuse metastases, probably from a primary growth in the breast.

The patient received supportive treatment, but the course was inexorably downhill and she expired May 7, 1945.

The necropsy revealed the following: Scleroderma of the hands, face, chest and abdomen was present. Metastatic carcinomatous infiltration—primary site unknown—involved the liver, pleura, right lung; the right hilar, tracheo-bronchial, and posterior mediastinal lymph nodes; the wall of the esophagus, the right adrenal, the right leaf of the diaphragm, and the lumbar spine.

The stomach, the small and the large intestine were normal. The esophagus showed chronic inflammatory changes, such as are seen in esophagitis. The epithelium was largely absent, and there was a diffuse, marked perivascular infiltration of lymphocytes with a few plasma cells in the propria and among the glands. The submucosa showed slight fibrous thickening. There were clumps of metastatic tumor cells in the lymphatics of the muscularis and the submucosa. There was medial hyperplasia of the small arteries and arterioles in all the layers of the viscus.

Case 5.—G. R., a 41-year old female, whose past and family history were irrelevant, entered the hospital January 3, 1941, complaining of pain in the fingers of the left hand. Her illness started 25 years ago with "muscular rheumatism" which confined her to bed for three months. At this time, her joints were stiff and painful, but not red or swollen. One year later, she noticed that the fingers of the right hand were becoming stiff, numb and cold. Twenty-three years ago, a diagnosis of scleroderma was made. She was treated with thyroid extract and received intensive radiation therapy to skin of the arms, chest and face. The involvement of the skin became progressively more severe, and finally involved almost the whole body. Shortly after the radiation therapy, red blotches developed on the arms, chest and face. In 1928, she suffered an attack of "rheumatic fever" which lasted three months and since then all the joints have become stiff and generalized pains have developed in the muscles and bones. At that time, she was told that her heart "was weak." In 1934, she was again hospitalized for "arthritis and scleroderma." Contractures had progressed to such an extent that she had been unable to walk for several years. Four weeks before admission, she developed pain in the left hand and a blackened area on the tip of the left middle finger appeared. For several years, she had had epigastric discomfort and belching mainly after meals, and three to five loose stools daily, usually in the afternoon. There was no blood, pus or mucus in the stools.

The physical examination revealed an individual possessing an appearance typical of generalized scleroderma, with marked sclerodactylia, and deformities of upper extremities. The lower extremities showed less involvement. There were calcific areas in the skin over both tibiae, with ulceration of the right leg, and gangrene of the tip of the left middle finger. Aside from the involvement of the skin, the head and neck were negative. The excursions of the chest were limited by the tight skin. The lungs were negative. The heart was enlarged by percussion, the left border being two cm. beyond the midclavicular line, in the fifth interspace. There was a loud systolic murmur at the apex, and a softer blow at the aortic area. The liver edge was felt two fingers breadth below the costal margin. The abdomen was otherwise negative. Reflexes were normal.

The laboratory data were as follows: The urine examinations revealed the presence of red blood cells on many occasions. The hemograms showed an anemia, the erythrocytes numbering from 2.5 million to 4.2 million per cu.mm. and the hemoglobin varying between 7.0 and 12.0 gm. per 100 cc. The leucocytes numbered from 6,500 to 8,500 per cu.mm. and the differential count was not remarkable. The fasting glucose was 93.0 mg. and the urea nitrogen 15.5 mg. per 100 cc. of blood. The serum calcium was 9.8 mg. and the phosphorus 3.7 mg. per 100 cc.

The Kahn and Wassermann reactions were negative, and the alkaline phosphatase was 3.0 Bodansky units. The basal metabolic rate was determined on several occasions and the results varied from plus 3 to minus 4. A biopsy specimen of skin from the legs showed chronic inflammation of skin and subcutaneous tissue, with hyalinization and focal calcification. X-ray examination of the skeleton showed generalized decalcification, with hypertrophic, arthritic changes involving the left shoulder, right knee, left elbow, and both hips. There were many calcareous deposits scattered through the soft tissues of the extremities most marked in the region of the joints. There were marked arthritic changes, with decalcification of most of the bones of the phalanges. Several of the phalanges were absent. Roentgenograms of the chest showed extensive pulmonary fibrosis. The Graham test was negative. Many examinations of the esophagus showed moderate dilatation, and marked rigidity of the organ. There was some narrowing just proximal to the cardia. While the mucosal pattern was normal there was little if any peristalsis. The emptying, in the erect position, was slightly increased. The diagnosis was generalized scleroderma with esophageal involvement.

Course in the hospital: The patient was treated with diathermy and other physiotherapeutic measures. In general, the treatment was symptomatic. With the passage of time, the skin became progressively more involved, and the contractures of the upper extremities more severe. The general condition slowly deteriorated. At the time of this writing, the patient cannot feed herself and is a helpless invalid.

Case 6.—G. S. a 54-year old man, entered the hospital August 26, 1948 complaining of stiffness of his fingers, shortness of breath and weakness. In December 1947 he noticed pain and stiffness of his fingers which on exposure to cold would become waxy and at times blue. He entered another institution in February 1948, at which time, on physical examination, induration and thickening of the skin over the knuckles, neck and abdomen were noted. A specimen of skin taken for biopsy proved on examination to be scleroderma. During the course of a right stellate ganglion block, a right pneumothorax occurred, with collapse of 95 per cent of the lung. Subsequently fluid was discovered in the right chest. Repeated cultures of the fluid were negative. X-ray examination of the lungs showed, beside the pneumothorax, fibrous scars in the right apex. Bronchoscopic examination was negative.

Upon discharge from the hospital, the patient noted increasing stiffness of the fingers, and other joints, especially the knees. In April 1948 he began to have difficulty in swallowing, the food seeming to stick in his gullet. About the same time attacks of palpitation appeared, usually in the morning.

On admission to this hospital, the patient appeared chronically ill, with tightness of the skin of the hands, forearms, face, neck, abdomen and feet. The skin changes were most pronounced over the bony prominences of the hands, where complete lack of mobility, gave the skin a leathery consistency. The fingers and toes were fusiform. There was loss of the normal skin folds and the finger points were shallow. The skin over the abdomen was brownish.

The heart was normal. There were diminished breath sounds at the right base posteriorly, and bronchophony was heard at the angle of the right scapula. The abdomen, difficult to palpate because of hardening of the skin, was negative. There was edema of both feet and ankles. The blood pressure was 140 systolic and 80 diastolic.

Laboratory data.—The blood urea nitrogen was 13 mg. per 100 cc. of blood. The glucose tolerance test gave the following values: The fasting sugar was 91 mg. at 30, 60 and 120 minutes the readings were 127, 156 and 150 mg. respectively. The alkaline phosphatase was 4.8 Bodansky units and the thymol turbidity was 2 units. The urinalysis was essentially negative and the stool was guaiac negative. Examination of the blood revealed the hemoglobin to be 10 gm. per 100 cc. The erythrocyte count was 3.4 million and the leucocytes numbered 9,500 per cu.mm. The differential count showed 75 polymorphonuclears, 18 lymphocytes, 4 monocytes, 1 myelocyte and 1 eosinophil per 100 cells counted. The plasma proteins were: total 5.70 gm., albumin 3.08 gm. and globulin 2.62 gm. per 100 cc.

Electrocardiographic examination showed a supraventricular type of tachycardia.

X-ray examination of the chest revealed loculated fluid at the right base with pleural thickening. Infiltrative changes of both apices were interpreted as old fibroid tuberculosis.

The esophagus was dilated and the walls rigid. Peristalisis was absent and there was retention of barium in the organ. The appearance was considered compatible with a diagnosis of scleroderma of the esophagus.

Course in the hospital. The patient is undergoing a course of hydrotherapy and is being treated symptomatically. The condition is at present stationary.

DISCUSSION

Scleroderma is said to occur in female twice as often as in males. In the cases reported in this paper five were females and one was a male.

The cause of scleroderma is unknown. There is an extremely rare congenital form known as the Werner syndrome, affecting children, in which the skin changes are accompanied by bilateral juvenile cataracts, premature greying of the hair and other endocrine stigmata.[11] Only thirteen cases have been described, three from this hospital. Scleroderma has been known to follow chronic arsenic poisoning, trauma,[12] frostbite,[13] routine inoculations.[14] The frequent occurrence of lesions of the glands of internal secretion has led some observers to incriminate the endocrine system.[15] The parathyroids, especially, have been ascribed an important role, on rather dubious grounds. Leriche and Jung considered scleroderma a form of cutaneous hyperparathyroidism[16] but ablation of these glands has produced disappointing results. Since arterial spasm of the extremities plays such an important part in the symptomatology of the disease, the sympathetic system has been thought to be involved and sympathectomy has been advocated.[17] It is of interest that case 3 which terminated fatally had a sympathectomy and a parathyroidectomy.

The disease, as a rule, runs an extraordinarily chronic course, though cases have been known to terminate fatally in a few weeks.[4] Ordinarily appearing during adult life, it can occur at any period from infancy to old age. The onset is usually insidious, though acute cases are not rare.[5] The evolution of the disease varies in different individuals. In some, the skin changes predominate, and the edema, induration and inflammation initiate a process which eventually results in a tight, hidebound skin, with areas of pigmentation and depigmentation. Extensive areas of calcification may be found in the skin and subcutaneous tissues, a condition which has been known as the Thiebierge-Weissenbach syndrome.[6] The color of the skin may vary from ivory to deep bronze, and while the mucous membranes escape pigmentation, the darkened skin frequently suggests Addison's disease. When the chest is affected, as in case 5, respiration may be interfered with. When the skin of the face is involved, the atrophied, boardlike skin, drawn tightly over the bridge of the nose and other bony prominences gives the face a birdlike appearance. The lips become stiff and indurated. The mouth puckered, and the lack of mobility makes alimentation difficult.

Other cases begin with symptoms strongly suggesting Raynaud's syndrome. The hands are especially involved, as in cases 1, 2, 3, 4 and 6, although the feet may also take part in the process, as in cases 2 and 6. The local asphyxia trophic disturbances—vesicles and ulcers of the skin, atrophy of bone, and disappearance of the terminal phalanges—and even gangrene of finger tips may occur. These changes are well illustrated in case 3. It is only when the skin changes become manifest that the true nature of the disease is discovered.

At some time or other, most cases of scleroderma develop arthritic changes, which predominantly involve the phalanges but which often affect other joints as well. Movements of the extremities may be interfered with to such an extent by the hardened skin that ankylosis results. The combination of fever, malaise, muscular atrophy and arthralgia mimics rheumatoid arthritis. In all of the cases described in this paper, arthralgia affecting most of the joints including the spine was an important part of the clinical picture.

The characteristic pathologic findings in scleroderma are proliferation of the connective tissue stroma leading to rupture and disappearance of elastic fibers and alterations in the small blood vessels. The latter show a hypertrophy of the smooth muscle of the media, with infiltration of the connective tissue fibers, a thickening of the intima and a narrowing of the lumen, or complete obliteration with thrombus formation. In the esophagus there is thickening of the collagen bundles in the submucosa, especially near the cardia. There are hyperplastic changes in the arterioles. The mucosa may show many ulcers, the bases of which are formed by the lamina propria, with extensive infiltration with plasma cells, lymphocytes and polymorphonuclear leukocytes. The connective tissue changes are not pathognomonic of scleroderma, but are also found in diffuse lupus erythematosus. The term "diffuse collagen disease" embracing the two diseases has been employed to indicate the fact that the essential morphologic changes are in the connective tissue.[7] Dowling[8] claimed that scleroderma and dermatomyositis are closely linked. Others[9] have gone even farther and have considered that the connective tissue and vascular changes were a "common denominator" in scleroderma, lupus erythematosus, dermatomyositis, and periarteritis nodosa, a view contested by Baehr and Pollock.[10]

The interpretation of the gastrointestinal symptoms in these patients is difficult. Unless the dysphagia and gastric distress are extreme or specifically inquired into by the physician, they may be subordinated by the patient. The thickening of the skin, the ulceration of the finger tips and the arthritis claim the patient's attention. However, very few patients go through the course of their disease without some gastrointestinal disturbance. It must be borne in mind, too, that these patients may have other diseases of the alimentary tract, having no connection with scleroderma but which contribute to the symptomatology. In case 2, although the patient complained of epigastric distress, a roentgen examination was unfortunately not performed. On autopsy a typical duodenal ulcer was found. Changes characteristic of scleroderma were also found in the esophagus and the stomach. How great a part the ulcer played in the patient's symptoms is difficult to say. In another case (case 4), the esophagus which was already affected by scleroderma, was found on autopsy to be infiltrated with tumor cells, the origin of which was unknown.

All of the six cases reported had demonstrable esophageal lesions, five on roentgen examination and one on post mortem. Case 4 in whom no symptoms of difficulty in swallowing were elicited showed the typical roentgen appearance of the esophagus.

Dyspeptic symptoms dominate the picture when the esophagus is involved. The patient suffers from sour eructations, epigastric distress, and a careful inquiry usually elicits a history of dysphagia which occasionally is present from the early stages of the disease. There are complaints of food sticking in the throat, and retrosternal pain.

The pathologic changes in the esophagus offer an explanation of the symptoms. The diffuse

sclerosis of the connective tissue interferes with deglutition. The dysphagia is caused either by the constriction of the esophagus which may stimulate a stricture, or more commonly by the stiffness and the loss of peristalsis in the lower two-thirds of the organ. The burning sensation and pain so often noted by the patient undoubtedly result from the esophagitis, an inflammatory process in the mucosa caused by the scleroderma, and analogous to the pathologic change in the skin. The regurgitation and retention of gastric secretions, especially when there is an ample secretion of hydrochloric acid, may cause in the already diseased mucosa a peptic esophagitis, similar to the condition described by Winkelstein.[25] The primary lesions are, however, sclerodermatous.

Roentgenologically, the appearance of the esophagus conforms to several patterns: There may be diffuse dilatation of the entire organ (A and B), or dilatation may occur proximal to an area of stricture (D). In some cases spasm may involve a large part of the esophagus, with dilatation above and below the spastic area (B). Extensive areas of spasm and induration may cause the barium to course through the esophogus in a spiral manner (C), or the esophagus may assume a saw-tooth appearance (E). In all cases in which the esophagus is affected by scleroderma, peristalsis is much diminished or entirely absent. There is no delay at the cardia. The esophagus, which has lost its normal pliability, remains gaping after the barium has passed through it. As a rule, the patent organ contains a large amount of air, and localized collections of barium may be seen, which probably represent areas of ulceration (D, arrow). The delay in emptying is best demonstrated in the horizontal position. The barium may remain in the esophagus for long periods and Jackson[25] has described a case in which the barium was retained for eight hours. When the patient stands, the barium enters the stomach more readily, indicating that the force which propels the bolus through the cardia is gravity rather than peristaltic action.

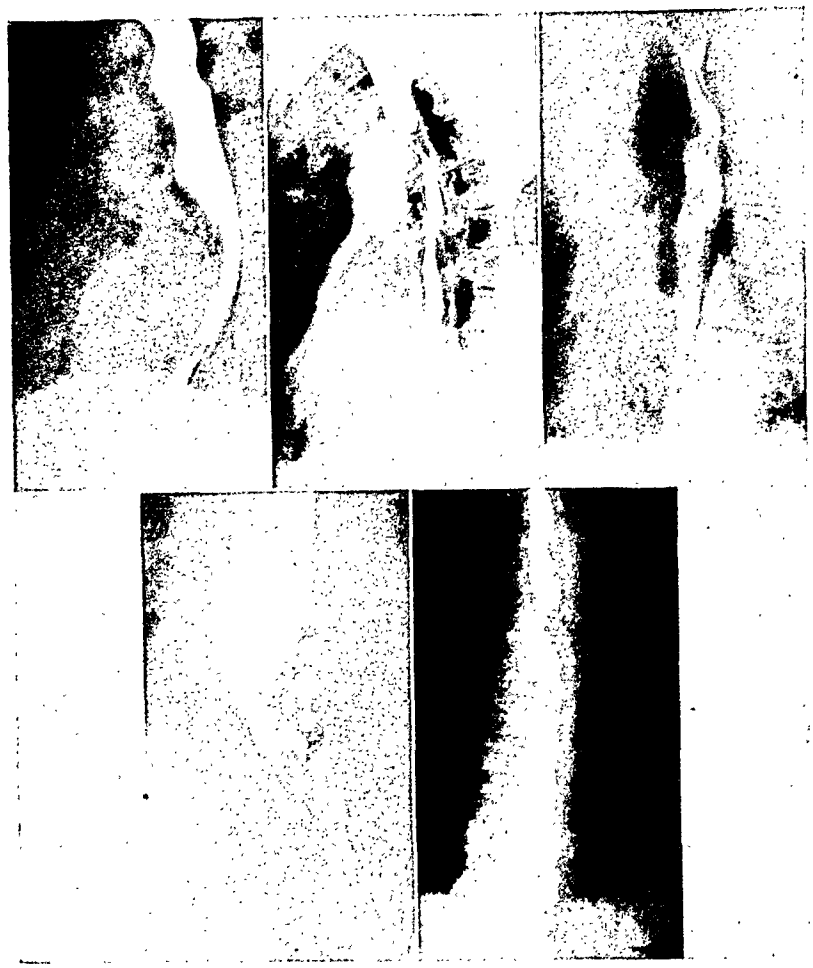


Fig. 1. Roentgenologic appearance of the esophagus in scleroderma. (Kantor, J. L. and Kasich, A. M., Handbook of Digestive Diseases, The C. V. Mosby Company).

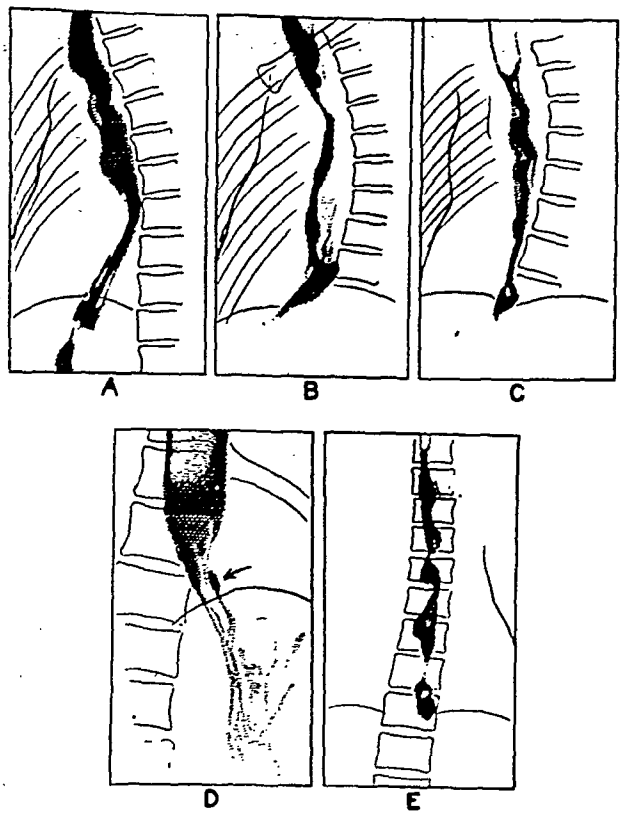


Fig. 2 Diagramatic representation of roentgenologic appearance of the esophagus in scleroderma. (Kantor, J. L. and Kasich, A. M., Handbook of Digestive Diseases, The C. V. Mosby Company).

Scleroderma of the esophagus may be confused with phrenic ampulla or cardiospasm. In phrenic ampulla the stricture moves along and is most prominent during the phase of regurgitation with the patient in deep inspiration, whereas in scleroderma the stricture is constant. Cardiospasm is differentiated from scleroderma of the esophagus by the fact that in the latter the stricture is usually above the hiatus, in contrast to cardiospasm in which the narrowing is at the hiatus. Furthermore, in scleroderma the esophagus seldom assumes the tremendous proportions seen in cardiospasm. In rare cases sclerodermatous ulcers of the esophagus may simulate primary peptic ulcer of the organ. Collections of gas may produce filling defects that resemble carcinoma. In general, however, the differentiation of these conditions is not difficult if the primary disease is kept in mind.

SUMMARY AND CONCLUSIONS

Six additional cases of scleroderma with esophageal lesions are reported. A post-mortem examination was performed on two patients. The symptoms and the roentgen appearance caused by the esophageal involvement are described. Stress is again laid upon the fact that generalized scleroderma is a disease, the visceral manifestations of which may be widespread and varied.

The author is indebted to Dr. David Unterman for the reports of the necropsy findings.

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NUTRITION

The Encephalopathy Of Hyperinsulinism

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THE effects of excessive doses of insulin upon the body have been under consideration ever since its isolation by Banting and Best in 1921. Opportunities for investigation of such effects are often seen in the course of treatment for diabetes mellitus. The Sakel method of shock therapy for schizophrenia directly induces hypoglycemia through the use of insulin. The occasional untoward results produced by this treatment have also been used for study. In addition, spontaneous forms of hyperinsulinism are seen produced by neoplasm, hypertrophy or functional over-secretion of the islets of Langerhans. Lastly, the effects of insulin overdosage have been studied in experiments with animals. Of primary interest in all investigations is the manner in which the central nervous system is affected.

Diabetes in the first and second decades of life is not infrequently an extremely labile form of the disease.[1] In this type satisfactory control often eludes the grasp of even the most careful and experienced clinicians. Very sudden and unpredictable swings from approximate control to complications are seen within the course of a few hours. The patient may suddenly develop glycosuria and acidosis or, conversely, suddenly incur severe hypoglocemia. In such cases the therapeutist constantly strives to find the insulin type, timing and dosage which will cause the fewest episodes of ketosis or shock. The factors responsible for such instability of insulin requirement are still not known. These patients, consequently, are frequently subjected to repeated, often severe episodes of hyperinsulinism. It appears that although they cannot live without insulin they do not live well with it.

We wish to report an incident of severe hyperinsulinism in just such a case of juvenile diabetes in which unconsciousness was produced for over 72 hours.

From The Medical Service of The Harlem Hospital
New York, N. Y.
Submitted November 8, 1948

CASE REPORT

G. B., a 15-year old colored girl, was admitted to Harlem Hospital at 11:30 A.M., March 3, 1947, in coma. The patient had severe, unstable diabetes from the age of 7 and required large amounts of insulin to approximate control. This was her 14th admission since 1941 to this institution alone. All admissions were due to poor diabetic control. Most of them were for varying degrees of acidosis but occasionally insulin reactions were the cause. No history of events leading up to coma was available at the time of admission.

Examination revealed stertorous respirations, unconsciousness with vigorous reaction to stimuli, B.P. 140/98, pulse rapid and full. The remainder of the physical examination was essentially within normal limits. The urine obtained by catheterization contained 4+ sugar, 3+ acetone, and no diacetic acid. Blood was immediately drawn for blood sugar and carbon dioxide combining power determinations; an I-V infusion of 5% glucose in saline was started and 30 units of regular insulin was administered. At 1:00 P. M. the blood sugar was reported to be "less than 50 mg%" and it was realized that despite the high content of sugar and ketone bodies in the bladder urine the present condition was insulin shock. 50cc of 50% glucose was immediately given intravenously. The patient became semi-conscious but shortly thereafter lapsed into her former state with light convulsions. At this time a catheter specimen of urine, presumably from a previously emptied bladder, contained 4+ sugar, no acetone. The infusion of 5% glucose in saline was continued and again the patient reacted, this time becoming rational enough to respond to some questions. Restlessness then caused displacement of the intravenous needle. At 3:00 P. M. the urine contained 4+ sugar, the blood sugar was again reported "less than 50 mg %" and the admission Co^2 combining power was reported as 64 vol.%. Soon after, the patient spontaneously voided approximately 500cc or

	HOSPITAL DAY	URINALYSIS* Sugar	Acetone	BLOOD SUGAR	CO_2 COMB. POWER	MENTAL STATE REMARKS
HYPOGLYCEMIC PHASE	1st DAY 11:30 AM	4+	3+	"Less than 50mg%"	64 vols%	Comatose: reacts to stimuli.
	1:00 PM	4+	0			Slight improvement after I-V glucose.
	3:00 PM	4+	0	"Less than 50mg%"		Spont voided over 500cc of urine.
	8:30 PM	0	0			Restless - comatose
	9:30 PM	0	0			Restrained - very restless.
	2nd DAY 2:00 AM	0	0			Ibid
	3:00 AM	0	0			Ibid
	10:00 AM	0	0	62mg%	58 vols%	Restless - phonating - then comatose.
	11:30 AM	4+	0			Non-responsive-hyperactive reflexes.
POSTHYPOGLYCEMIC PHASE (NORMO - TO HYPER - GLYCEMIC)	3:00 PM	4+	0	175mg%	40 vols%	Restless - irrational.
	8:00 PM	4+	0			Ibid
	3rd DAY 3:00 AM	4+	0			Ibid
	9:00 AM	4+	0	290mg%	38 vols%	FOCAL NEUROLOGICAL SIGNS.
	2:30 PM	4+	0	265mg%		Arousable but irrational.
	5:00 PM	4+	0			Ibid
	8:30 PM	0	0			Restless - noisy - restrained.
	10:30 PM	0	0			Sensitivity to small doses of insulin.
	4th DAY 2:30 AM	3+	1+			Restrained.
	9:00 AM	4+	0	395mg%	39 vols%	Clear and fully oriented.

* No diacetic acid present.

more of urine following which the bladder was now determined to be completely empty. Subsequently urines were all sugar free (see table).

During the next 18 hours the patient remained in insulin shock of varying depth depending on the amount of glucose being instilled intravenously at the time. It was impossible to keep an intravenous infusion running more than 20 to 30 minutes due to poor veins and marked restlessness of the patient, particularly as shock lightened. Close restraints were required and even these were almost insufficient. In this period roughly 50-70 Grams of glucose were given intravenously.

At 10:00 A.M., March 4th, the second hospital day, the urine was still sugar free, the blood sugar was 62 mg % and the CO^2 combining power was 58 vols.%. The patient was again deeply comatose and non-responsive. The respirations were slow, deep and regular, pulse 112 per min. and of good quality, B.P. 120/80, rectal temp. 101.2°F. Neurological examination revealed equality of pupils with reaction to light. The deep reflexes were equal but markedly hyperactive. There was no apparent motor weakness. Further history was now obtained from the girl's mother: for 2-3 weeks the patient had been having frequent light "shocks" in the early morning on a dosage of 90 units of globlin insulin before breakfast and 60 units of globulin insulin before supper. She had found her daughter unconscious in the morning following an evening of strenuous dancing.

Heroic measures were now instituted to raise and maintain the blood sugar above hypoglycemic levels. An arm vein was phlebotomized, 50cc of 50% glucose infused and the arm was restrained manually for over 2 hours while a rapid infusion of 10% glucose in saline was given. After 1½ hours of this therapy the urine contained 4+ sugar. By 3:00 P.M. that afternoon the blood sugar level was 175 mg % with 4+ (!) sugar in the urine. Despite the attainment of hyperglycemia the patient's condition improved only slightly. Although she would open her eyes on stimulation there was no response to questions and no orientation or recognition of her very familiar surroundings.

On March 5th, 48 hours after admission, this mental state remained essentially unchanged. The blood sugar level was 290 mg %, urine sugar 4+, and no ketone bodies were present in the urine. Careful neurological examination revealed hyperactive but equal reflexes, slight widening af the right palpebral fissure with slight flattening of the right nasolabial fold and suggestive motor weakness on the right. A positive Babinski was elicited on the left with equivocal Babinski on the right. During that day restlessness and unconsciousness continued. Toward evening she suddenly became violent, stood up in bed shouting loudly and was again restrained with difficulty. Small doses of regular insulin were now being given at intervals (see table). The following morning, 72 hours after admission, the patient was mentally clear and alert with no recollection of any events during the past 3 days. Neurological examination now revealed abdominal reflexes on the left greater than on the right, deep reflexes on right greater than on left and Babinski reflex negative bilaterally. The blood sugar level was 395 mg % and more adequate insulin therapy was instituted. The remainder of the hospital stay was characterized by the usual difficulty in establishing control of glycosuria and avoiding shock. In part the frequency of the latter was explained by the finding of a lowered renal threshold. She was discharged finally on an insulin dosage of protamine zinc insulin units 75 and globin insulin units 115 before breakfast daily, still spilling 3+ sugar during most of the day. No residual abnormal neurological findings could be found at the time of discharge. In the year since discharge she has been admitted twice for mild acidosis. Each time she has been found to be bright, alert and with no impairment of mentality. An electroencephalogram taken April 15, 1948 exhibited no abnormal brain waves.

DISCUSSION

The case reported above exhibits many interesting features. First, it should be noted that the urine examined on admission contained large amounts of sugar and acetone yet blood chemistry studies taken simultaneously showed marked hypoglycemia and a normal CO^2 combining power. This indicates that apparently asymptomatic acidosis had immedately preceded insulin coma. These patients seem to develop "tolerance" to acidosis. Ketonuria which in other diabetics would be correlated with vomiting, drowsiness and stupor is often seen without definite clinical symptoms. This has been called "'laboratory acidosis" to distinguish it from acidosis with the usual clinical picture. It should not be treated as vigorously as the latter. Since the bladder evidently was not emptied by the patient before the pendulum rapidly swung to the hypoglycemic side the urine still contained sugar and ketone bodies. In this instance, therefore, the urine was an entirely unreliable indicator of the true condition present. Without previous knowledge of the patient and her history temporary diagnostic confusion on the part of the admitting physicians is understandable. The second feature of interest is in regard to the hyperinsulinism produced by slow acting insulins. Globin insulin although intermediate in action time between regular and protamine zinc insulin may, when given in large doses every 12-24 hours, as in this case, overlap in action and form depot stores much in the manner of protamine zinc insulin. The patient had been placed on two daily doses of globin insulin in an effort to eliminate early morning shocks which were difficult to avoid on protamine zinc insulin. No doubt large depots of globin insulin had accumulated. In treating a patient in insulin shock due to a slow-acting insulin, glucose administration must be continuous and adequate over a sufficient period of time to permit all accumulated stores of insulin to be completely utilized. The administration of a single dose of 50% glucose intravenously may restore consciousness but as glycogenesis proceeds rapidly in the liver under the influence of the insulin still present in the body the blood sugar level again drops and shock recurs. This may happen a number of times if glucose is discontinued each time as soon as consciousness returns. In the case reported difficulty was encountered during the first 18-20 hours in administering adequate and continuous intravenous glucose. The patient was moderately obese with poor veins and repeatedly caused stoppage of infusions by violent movements. These factors considerably impeded the return of

the blood sugar to normal or hyperglycemic levels.

Of further interest was the occurrence of continued unconsciousness for 48 hours after the elevation of the blood sugar to hyperglycemic levels. The encephalopathy of hyperinsulinism may therefore be divided into an initial hypoglycemic phase and a secondary, post-therapeutic, normoglycemic or hyperglycemic phase. In this patient focal neurological signs did not become evident until the hyperglycemic phase was reached. These signs were indicative of organic cerebral damage.

That definite injury to the central nervous system, both temporary and permanent, is produced by hyperinsulinism is adequately affirmed by numerous investigators. In patients who died in insulin shock Bowen and Beck reported cerebral edema grossly, and histologic changes ranging from moderate to severe degeneration of ganglion cells in the cortex and basal ganglia.[2] Terplan reported "Nissl's severe change" in the neurons and swelling phenomenon of the glia and axis cylinders.[3] Grayzel produced hyperinsulinism in rabbits and found diffuse and focal types of parenchymatous degeneration in the cortex and basal ganglia.[4] The severity and acuteness of the changes depended on the frequency and intensity of the convulsions produced. In recent years a number of similar and confirmatory reports have appeared.[5]

The manner in which hyperinsulinism produces damage to the brain is not known. Many theories in regard to the pathogenesis have been advanced. The phenomena of hypoglycemia, anoxemia, anhydremia, alkalosis and other metabolic disturbances accompanying hyperinsulinism have each been held responsible. Malamud and Grosh disputed the primary role attributed to the hypoglycemia in view of the lack of parallelism between the level of the blood sugar and the clinical manifestations.[6] They and others[7] dispute the theory that hypoglycemia causes vasospasm during seizures with resultant stasis, thrombosis and hemorrhage because the histopathologic picture is inconsistent with that hypothesis. For similar morphological reasons these investigators maintain that the theory that hypoglycemia produces sufficient cerebral anoxemia to cause the damage is untenable. Undoubtedly impaired oxidation of the brain does accompany hypoglycemia but this does not explain the clinical manifestations nor the histopathologic changes. Drabkin and Ravdin advanced the theory of cerebral edema in demonstrating a relationship between convulsions and anhydremia produced by insulin.[8] However, other clinical manifestations remain unexplained. Pathologico-anatomically one would expect cerebral edema would be more frequent in hyperinsulinism than is the case. Moreover it is doubtful if edema can produce such degeneration of nerve tissue.

The assumption of a direct effect of insulin on the neurons finds several advocates. It is known that insulin in large doses, producing hypoglycemic shock, interferes with the utilization of oxygen and dextrose by the gray matter of the brain. This was demonstrated in animals by Holmes[9] and in man by Dameshek et al.[10] One might think therefore that "intracellular anoxemia" or the inability to utilize oxygen in the presence of large doses of insulin. may be responsible for the severe, generalized disease of the neurons following prolonged and repeated episodes of hyperinsulinism. Malamud and Grosh point to the purely parenchymatous degenerative character of the anatomic changes as the outstanding feature.[6] All the characteristics of a primary toxic degenerative process are obvious from the direct and diffuse effect on the parenchyma beginning with "acute swelling" of the neurons and paling of the tissue and progressing to ultimate degeneration, to which the glia reacts secondarily. The condition, they claim, is analagous to primary degenerative diseases of the central nervous system and to encephalopathies due to exogenous toxins (e. g. morphine or nitrous oxide). They suggest a direct toxic effect of some substance elaborated in hyperinsulinism and speculate that the excess insulin itself may act as such a toxic substance. Olmsted and Taylor conclude that the convulsions following insulin administration cannot be attributed to the "mild anoxemia" produced but that both phenomena are directly caused by insulin.[11]

Others have attributed the changes to the hypoglycemia directly through diminished nutrition of the brain cells.[12] It is generally agreed that dextrose is essential in the normal utilization of oxygen by brain tissues. A possible explanation for the reversibility of even marked neurological manifestations is that the nutritive requirement for function of the brain cells is far greater than that required for life and maintenance of structure.[12a] At present the consensus of opinion appears to be that the cerebral changes and resultant symptoms are due either to hypoglycemia directly or to a direct toxic action of insulin which causes diminished cellular nutrition and the impaired utilization of oxygen (intracellular anoxemia). In either event serious interference with cellular metabolism is produced.

The variable clinical picture produced by hyperinsulinism which proceeds to the stage of organic neurological symptoms (convulsions, periods of coma and focal signs) and psychopathologic manifestations (psychotic states) has been described under numerous headings and titles which usually emphasize the extent of obvious and irreversible damage.[13] We offer the term **Encephalopathy of Hyperinsulinism** as one which is applicable under either of the two favored theories of pathogenesis to a clinical syndrome of coma and convulsions

which, if not fatal, may vary in late manifestation from recovery without clinical residua (with or without latent damage) to recovery with complete mental deterioration.

SUMMARY

1. A case of severe hyperinsulinism in a juvenile diabetic is reported in which unconsciousness was produced for over 72 hours.
2. Emphasis is placed on the unreliability of the urine as an initial diagnostic indicator in coma seen during the course of extremely labile diabetes mellitus.
3. Globin insulin, in large doses, is shown to have a cumulative, storage effect similar to protamine zinc insulin. Hyperinsulinism produced in this manner must be treated continuously with parenteral glucose until the depots are practically exhausted.
4. A brief review of the pathological changes which produce the clinical syndrome and of the various theories regarding their pathogenesis is presented.
5. The term ENCEPHALOPATHY OF HYPERINSULINISM is offered as a broad, all-inclusive one, which covers all the varied clinical manifestations seen.

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Nutrition Notes And Abstracts On Nutrition

THE ANTI-THYROTOXIC EFFECTS OF VITAMIN B_{12}

Thus far (July, 1949) no reports have appeared which might indicate any long-time failure of vitamin B_{12} to maintain patients with pernicious anemia in satisfactory hematological and neurological remission, provided the substance is intramuscularly administered in sufficient doses. It has already been noted that persons suffering from pernicious anemia, complicated by severe hypothyroidism, may require higher dosage of thyroid extract than they needed prior to liver therapy. In some cases the dose has needed to be doubled to maintain a normal basal metabolic reading. That this phenomenon depends upon an anti-thyrotoxic influence of vitamin B_{12} itself now becomes clearer. Ershoff* found that feeding liver combats thyrotoxicity in rats. It is now known that minute amounts of the new vitamin, in animal experiments, duplicate the growth properties of either fish solubles or injectable liver extracts in animals who are receiving thyrotoxin. It is not impossible that vitamin B_{12} may eventually find a sphere of usefulness in the treatment of hyperthyroidism, although further investigation must precede its use clinically for this purpose. In the interim, the practioner should bear in mind that the administration of thyroid extract is less effective in patients who are being treated either with liver extracts or vitamin B_{12}.

A PLUG FOR ACID THERAPY

Reba L. Edwards, M.D.,* found achlorhydria in all four cases of angioneurotic edema which she critically examined. She states that over fifty percent of cases of dermatoses seen by her showed an altered gastric acidity. In the described cases of acne, seborrhea and seborrheic dermatitis, the acid levels should not be regarded as truly low. It would be very interesting, however, if more cases of angioneurotic edema could be analyzed, preferably by the fractional test meal, as her report at least suggests the possibility of a marked acid reduction in these instances. An equal control series of normals and of other forms of skin lesions should be employed because it is not generally realized how common hypoacidity is among the adult population. It is fairly common with dermatologists to find hypoacidity in association with acne rosacea and it is already known that the administration of acid, as liquid or capsules, appears to assist control of this skin condition. How it does so is obscure, especially in view of the fact that today we regard chemical digestion in the stomach as of so little importance. It is well known, however, that the administration of large amounts of dilute HCl, of the order of 6 drams daily, alters the putrefactive flora ordinarily dominant in the upper gut of achlorhydrics. Even so it is difficult to see how this could be of benefit to a skin condition. The use of dilute HCl, under any circumstances, has recently begun to fall into disrepute, largely on theoretical grounds, but there remain capable internists, as well as dermatologists, who believe such therapy has given sufficient practical evidence of benefit to the body as a whole to justify its continuance. Theories have almost always carried less immediate weight than facts with the practitioner, and we are indebted to Miss Edwards for calling our attention to the apparent good effect of acid therapy in a group of dermatoses.

*Ershoff, B. H., Proc. Soc. Exp. Biol. Med, 64, 500 (1947)

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NUTRITION PROGRAM FOR WESTERN EUROPEAN CIVILIANS IN WORLD WAR II*

Major Leone makes the important point that, in case of further war, the U.S. Army Medical Department has learned the essential points in determining food requirements for all types of civilians, both in liberated and in conquered territories, and this knowledge should be at once put into effective use. Probably the chief achievement from D-Day onward in Europe has been to impress Army commanders and civilian authorities of the necessity of a definite nutritional program. He recounts the history of the effort of U.S., British and other United Nations from 1944 onward to establish a working scheme for determining the nutritional requirements of any given population and a study of this report indicates that insufficient importance was at first granted to nutritional studies by some of the Commands, although eventually all were able to see the importance of facilitating this work. The higher authorities had to be convinced that a definite nutrition program was important. Nutrition surveys, detailed surveillance, and nutrition standards were in crying need of being established and all this could not be left merely to the quartermaster as a simple problem in providing food. The Surgeon General was finally convinced of the importance of a well-organized nutrition program for the European Theater of operations. The first food tables agreed upon represented low rather than mean or optimal values. Leone points out

*Condensed from an article by Major N. C. Leone, M. C., in Bull. U. S. Army Med. Dept., April 1949.

that in case of an atomic attack, isolation of large or small groups of people may result, and survival might depend upon autonomy of such groups in matters of food supply. There seems no doubt that it required too long a time for the authorities to realize the great importance of scientific rationing in European areas. Ultimately the Germans were not permitted calories in excess of those enjoyed in liberated countries. For very heavy workers, 2,800 cal. per day was a maximum allowance and normal consumers were given 1550 cal. It was found that these figures provided a minimum safe diet, which preserved health and weight, provided the number of calories per day were not lowered below this level.

One of the essentials is the direct control of nutritional personnel and a centralized system of reporting so that, when desirable, data from various regions can be readily consolidated. He emphasized the importance of weighing persons, as an excellent guide to their nutritional states. Special rations ought not to be provided for special groups as this destroys morale among groups not receiving them. Oral administration of protein hydrolysate did not give satisfactory results. That the nutrition program succeeded at all is remarkable when one considers the constant administrative difficulties encountered. If war comes again, a program based on experience ought to be at once established.

Editorial: DID YOU KNOW? (Nutrition News, April 1949, Vol. 12, No. 4, p. 16).

Pies with an ice cream "crust" are now on the market The average length of life of prehistoric man was probably 18 years....A pound of butter requires 9.77 quarts of milk....Indigestion was treated in 80 A.D. by finely ground cooled lava from Vesuvius....Enough milk is produced each year in America to fill a river 3000 miles long, 3 feet deep and 40 feet wide.

BEFFA, M.A.: *Food habits in Lebanon.* (Nutrition News, April 1949, Vol. 12, No 4, p. 15).

Most Arab dishes take hours of preparation and are mixtures of foods. Turkish or Arabic coffee is served early in the morning. Many use hot milk for breakfast, in fact all milk must be boiled because of bacterial contamination, but one soon grows accustomed to it. Common dietary articles are cheese, olives, lebni and leban. Leban is made from coagulated milk with yeast added and permitted to ferment 12 hours. Lebni is leban with the whey removed. Lebni is usually mixed with olive oil. Bread, which is the staple of the diet, is produced in tasty flat rolls. At the noon meal, mutton is the chief meat used, often mixed with burghl, a whole wheat product, to make Kibbee. Vegetables stuffed with meat and rice is a favorable dish. Rice forms the basis of the diet and is served with stews. Real ice cream is unknown.

DAY, L. A., HALL, B. E., AND PEASE, G. L.: *Macrocytic anemia of pregnancy refractory to* neurological phenomena in dogs. In combatting atomic *with folic acid: report of case.* (Proc. Staff. Meet. Mayo Clin., Mar. 30, 1949, Vol. 24, No. 7, 149-157)

A woman of 27 at the beginning of the 7th month of her second pregnancy developed a severe macrocytic anemia which did not respond to liver extract nor to vitamin B_{12}, in dosage of 27.5 micrograms in 8 days. In fact, after each injection of vitamin B_{12} nausea and vomiting occurred . Excellent results were obtained by using folic acid, 15 mgm. per day, resting one day a week. A reticulocyte response of 18 per cent occurred on the sixth day of treatment. Within 3 days following the initial dose of 30 mgm. of folic acid, diarrhea ceased and edema began to disappear and a voracious appetite returned. Thirty days after beginning folic acid, she was admitted in active labor and this was uncomplicated. Post-partum course was uneventful. On the sixth post-partum day, hemoglobin was 12.1 gms., erythrocytes 3,750,000. The peripheral blood picture was normocytic and normochromic. This experience certainly suggests that the macrocytic anemia of pregnancy is due to folic acid deficiency. Five days before delivery the urinary assay indicated the 17-ketosteroids and estrogen decidedly low, while chorionic gonadotropins were at a high normal. The authors point out that these hormonal findings may be of great signicance and should be further studied.

JOHNSON, R. E.: *The Army's Medical Nutrition Laboratory.* (Nutrition Rev., March 1949, Vol. 7, No. 3, 65-66).

The whole aim of the Army's Medical Nutrition Laboratory is to assist the Medical Department of the Army in assuring that the troops are healthy and well-fed. Since soldiers are medically not different from civilians, the results of the laboratory's work are directly applicable to many problems in practice. The activities of the Laboratory have expanded considerably since V.E. day. One of its missions is to be in a position to observe and make recommendations on the nutrition and health of civil populations under military control. The health of troops in all environments has been studied, in the desert, in the aretic and subarctic, in the mountains and in India and Burma. Clinical investigation is proceeding on liver disease, neurological disorders, anemia in relation to chronic infection and vitamin A metabolism in lung disease. The Medical Dietetics Divison has attacked the problem of devising palatable high protein diets without unduly increasing the bulk and caloric content of the diet. Their general philosophy has been to increase the protein content of all items of the diet so that the patient if he eats anything will receive a high protein diet. The best dietary methods for rehabilitation of starved human beings is also under study. In connection with the study of anemia in relation to infection, an interesting finding is that the degree of anemia in patients with osteomyelitis is determined not by the total bacterial count in the wound but by the number of different species of bacteria present. Several papers have been produced on agene-induced *vitamin B_{12} therapy: response to treatment*

bomb injuries, the only therapeutic measures suggested to date, other than surgical, have been nutritional in nature.

WOLFSON, W. Q., COHN, C., LEVINE, R., ROSENBERG, E. F., AND HUNT, H. D.: *Liver function and serum protein structure in gout.* (Ann. Int. Med., March 1949, Vol. 30, No. 3, 598-614).

Sensitive liver function tests indicated that gout is not uniformly associated with functional hepatic impairment, and consequently diffuse liver disease cannot be the cause of gout nor an inevitable consequence of gout. In uncomplicated interval gout, abnormal liver function tests are rare. Most of the abnormalities are found in patients with known complicating diseases, and in these cases hepatic impairment is proportional to the nature and severity of the associated disease. In gouty arthritis, abnormal findings occasionally are present, but since serum globulins are produced by the entire reticulo-endothelial system, these findings cannot alone be taken to indicate hepatocellular involvement, but are due to general irritation of the reticulo-endothelial system. Values for serum total protein and for the individual serum protein fractions are normal in uncomplicated gout, and serum cholesterol values and partition also are usually normal. Hence all evidence suggests that diffuse hepatic involvement and alterations in circulating protein are not fundamental to the pathogenesis of gout.

MURRAY, W. G. D.: *Hyperinsulinism due to an islet-cell adenoma: a cure, with metabolic studies before and after operation.* (Brit. Med. J., March 26, 1949, 521-523).

A woman of 40 had been having difficulty waking in the morning and also periods of drowsiness. The attacks were characterized by negativism, perseveration and chattering. Hyperinsulinism was diagnosed by glucose tolerance tests and insulin tolerance tests, as recommended by Fraser and Smith. At operation a tumor 2 cms. in diameter was found on the lower border of the pancreas just between the body and tail and was removed. It proved to be a benign islet-cell tumor. The author emphasizes the usefulness of the Fraser-Smith intravenous insulin test in the differentiation of hyperinsulinism from other causes of hypoglycemia.

LEE, J., NAIDOR, D. AND TORRENS, J A.: *Diabetic coma: treatment with and without the early administration of glucose.* (Brit. Med. J., April 2, 1949, 564-568).

The authors studied 28 consecutive cases of diabetic coma, treated with and without the early administration of glucose. Ten cases received glucose, and 18 only saline in the first 4 to 6 hours of treatment. The two groups of cases were comparable. There was a mortality rate of 40 per cent in the glucose cases and 11 per cent in the saline cases. It appears that giving glucose in the early stages of the treatment of diabetic coma interferes with rapid rehydration and significantly increases the mortality.

CHAPPEL, G. M., AND HAMILTON, A. M.: *Effect of pressure cooking on vitamin C content of vegetables.* (Brit. Med. J., April 2, 1949, 574-575).

A comparison was made of the effect upon the retention of vitamin C in 10 different vegetables when cooked in a modern pressure saucepan and in an ordinary saucepan according to recommended methods. On the average the retention was higher in the vegetables cooked in the pressure cooker.

BROWN, A.: *Glossitis in pernicious anemia: effect of synthetic vitamins of the B. Complex.* (Brit. Med. J., April 23, 1949, 704-706).

Seven persons with Addisonian pernicious anemia each had a sore, red, raw-looking tongue in spite of the fact that their blood was responding to apparently adequate doses of liver extract. In those cases in which the type of extract used is mentioned, and presumably in all 7 cases, it was a refined liver extract, viz. anahaemin. One patient had angular stomatitis and vascularization of the cornea. In each case it was found possible to control these changes with a single member of the vitamin B complex in pure form. Four cases of glossitis responded to calcium pantothenate, and one each to nicotinic acid and folic acid. One case responded first to nicotinic acid and later to riboflavin. The patient exhibiting glossitis, angular stomatitis and corneal vascularization responded to riboflavin. It is suggested that the epithelial changes described reflect a breakdown in some metabolic system which may be similar to that responsible for the megaloblastic marrow and the neurological complications of the disease. Usually, many clinicians have regarded the persistence of glossitis as evidence of insufficient specific therapy (liver extract) but perhaps there may be a more complex explanation. The possibility of a combination of minor defect of absorption in pernicious anemia and a sub-optimal post-war dietary cannot be entirely discounted. Certainly the author correctly regards his experience as unusual because others have not encountered so many cases of persisting glossitis in cases which, as viewed from the hematological angle, were receiving adequate treatment. One case was given unusually large doses of liver extract (4 c.c. of anahaemin twice weekly, presumably 120 units per week), but in spite of this the glossitis persisted but responded eventually to riboflavin, 5 mgm. daily. Presumably vitamin B_{12}, which is effective against the anemia, the neurological changes and the glossitis, may promote the utilization of certain other essential substances, some of which are well known vitamins of the B complex. This is the first report in which pantothenic acid has been found to influence signs and symptoms in Addisonian anemia, and, since it is wide-spread in nature and foods, a deficiency would require to be conditioned in association either with absorption or utilization difficulties. In 4 of Brown's cases, calcium pantothenate was found by experiment to heal the glossitis. In 2 cases riboflavin was successful and this applies to the cases of corneal vascularization. In one case, folic acid controlled both the anemia and the glossitis.

In 6 of the cases, trial periods with the various vitamin B elements were employed, until the effective one was discovered. Once this was found, it had only to be continued a comparatively short time until the glossitis remained under control without further administration of anything except the liver extract. This fact suggests that in these cases a subsidiary enzyme system had been activated by the administration of pantothenic acid or riboflavin, which, once started, remained actively in effect. As no mention is made in any of these cases of neurological involvement, it may be assumed that none of them had severe neural degeneration or spinal cord alterations. If that be the case, then the author's speculation that the breakdown of some metabolic system, involving pantothenic acid, and riboflavin, might be similar to that which is responsible for the blood and cord changes, appears unwarranted. In fact, in most of these cases which he describes, hematopoiesis was progressing quite satisfactorily on liver extract alone and there is no evidence that the B factors improved the blood picture. The point of great value in this paper is that it presents pretty conclutive evidence of some sort of "dissociation" between marrow changes and changes in the oral mucosa. It would be particularly valuable if the author could explain the extremely unusual fact of at least 6 cases in which the glossitis failed to respond to liver extract in adequate doses because such cases are rarities.

Editorials

GIVE US MORE NUTRITIONISTS

One of the real needs of America today, and indeed the world at large, is a greater number of highly trained nutritionists. All authorities feel that while a great deal has been discovered with respect to food and health, the surface of the subject has been barely scratched. As W. H. Sebrell, Jr.* recently remarked, "If the world production and use of food can be based on freedom from want for everyone everywhere, we can have an age of health and prosperity exceeding anything ever known". Sebrell is not a dreamer but is director of the National Institute of Health, United States Public Health Service. The world has already endorsed the democratic principle that everyone is "entitled to an opportunity to secure a diet adequate for health", and that it is the responsibility of governments to assure this basic human right.

Few will take exception to this position, yet to designate a "right" and to fulfill it are very different assignments, even for governments. Educational problems are involved as to how to make known to the people presently available nutritional knowledge. Ignorance is the real reason why deficiency diseases continue to create a heavy morbidity and a staggering mortality. Administrative problems are involved all the way from school lunch programs and industrial lunch programs to the acute problem of how to feed the world today without injuring our own health in America. Agricultural problems are involved with respect to the culture of better vegetables, better cereals, and better fruits. But perhaps, above all, some way must be found to make more attractive to the young scientist the field of expert nutrition. So long as we advance in sound knowledge and valuable discovery, we may expect the rest to follow with less difficulty.

*Sebrell, W. H., Jr. We need more nutritionists, (Nutr. Rev., April 1948, Vol. 6, No 4, 97-99).

Book Reviews

UNDERSTAND YOUR DIABETES. *By John W. Caldwell, M.D.*, Oxford University Press, 146 pages, $1.50.

This book ranks high among the popular books written by physicians for those patients who suffer from some one definite disease. A number of "primers" have appeared on diabetes during the past few years but none excels Dr. Caldwell's book because he has herein given the diabetic all the information he can possibly need or use, but without confusing him by unnecessary material. It is possible that the diabetic intellectual might desire to pursue the subject into some of its scientific ramifications for his own satisfaction, but the average patient will be content to learn the danger areas of the disease and the methods of staying well. Dr. Caldwell has omitted nothing of importance and yet has succeeded in producing a succinct, valuable and highly readable book. It may safely be recommended by any physician to a patient suffering from the disease. The appearance of such a book is not only welcomed by the public for its utility value, but today it is also welcomed by the medical profession who are convinced that until "popular medicine" is written by doctors of medicine rather than by the professional writers, the public will continue to derive a slightly erroneous attitude toward the disease. Such a risk is utterly eliminated in Dr. Caldwell's valuable contribution.

BLAKISTON'S NEW GOULD MEDICAL DICTIONARY ($8.50). The Blakiston Company, Philadelphia, 1949.

It is claimed that this is the first completely new medical dictionary in 38 years and is the result of five years of intensive work by over 100 authorities. This is said to be the first medical dictionary to be compiled by a group of Editors working with an editorial board, the Army Medical Library and a university. It is a most modern and comprehensive compendium of terms employed in all branches of medicine, but it includes also the allied sciences, physics, chemistry, dentistry, pharmacy, nursing, veterinary medicine, biology, botany and medicolegal terms as well. Gould brought out "A New Medi-

cal Dictionary" in 1890, his "Dictionary of Medical Terms" in 1904 and since then there have been numerous editions of "Gould's Medical Dictionary", but the present volume is not merely a new edition, for it represents so complete a revision and so much addition as to constitute a new work. The searching for modern neologisms and new meanings involved thousands of hours of research, and the editors were able, for the first time on a project of this kind, to assemble a distinguished staff of 80 contributors all of whose names are extremely well-known in their respective fields. It is not only a very ambitious work but a sensible one. Thus the weight of usage is considered dominant and overbalances the Basle Nomina Anatomica and the British Revision in instances where the old terminology appears to have remained the "people's" choice. Unquestionably the medical profession have been in urgent need of a new lexicon for some years, so presumably no recommendation is needed, but is heartily given in any case.

OBESITY. *By Edward H. Rynearson, M.D., F.A.C.P., and Clifford F. Gastineau, M.D.*, 135 pages, ($3.50), Charles C. Thomas, Springfield, Ill., 1949.

This volume possesses a high "debunking" value. The literature, from the clinical aspect, is adequately reviewed, and perhaps every question that might present itself in treating a fat person is dealt with. Many superstitions are laid low,—in fact the general teaching of the book is that people become fat from overeating and lose weight by eating less. All endocrine causes of adiposity are denied, or regarded as unproved. The authors make it clear that obesity is a dangerous condition. An adipose person who reduces to a normal weight will probably never be as well as he would have been had he not ever been obese. Hunger and appetite are not differentiated for the present purpose, but it is emphasized that the mechanism which determines appetite is a primary factor in the development of obesity. The fat person has a higher rate of metabolism than normal even if his basal metabolic reading is normal, which will become plain if his normal ideal weight be substituted in the calculation. That is one reason why the use of thyroid extract is dangerous in reducing persons whose B.M.R. is normal. People fool themselves with respect to the estimated amount of food they eat, so that dietary histories are fallacious. Under controlled conditions, in a metabolic ward, weight-increase and weight-loss are mathematically and accurately predictable in time, and this is true whether or not the adiposity is complicated by the presence of some endocrine disorder. When damage to the hypothalamus occurs from any cause (encephalitis, brain tumor, injury) adiposity may result. Psychic conflicts induce adiposity because the individual overeats as a compensation for unhappiness. It is an integral part of the physician's duty to assist the patient psychologically as well as physiologically. "Heart disease and hypertension should not be considered contraindications but rather as urgent reasons for reduction". While this teaching is contrary to common medical practice, it deserves consideration. There is no such thing as excessive gastro-intestinal absorption. A reduced specific dynamic action as an explanation for adiposity is also denied, because of lack of evidence. It cannot be shown, either, that obesity may result from water retention. Hepatic cirrhosis and active peptic ulcer and Addison's disease are pretty definite contraindications to reducing. Coronary disease ought not to contraindicate reduction, since catastrophes do not follow the practice. The section on diets is especially valuable and the Boothby Food Monogram is included. The reviewer has never read quite so satisfactory a book on obesity, for the practitioner and recommends it with enthusiasm.

General Abstracts Of Current Literature

ROSSMILLER, H. R. AND ENSIGN, W. G.: *Hepatitis associated with undulant fever, report of a case.* (Cleveland Clinic Quart., Oct. 1948, Vol. 15, No. 4, 184-185).

A male patient aged 33 is described in whom hepatitis with liver enlargement was associated with proved Brucella infection, and who made a rapid and complete recovery on treatment with a combination of streptomycin 0.5 gms. and sulfadiazine 1.0 gm. every six hours for approximately 40 doses of each, and a high carbohydrate, high protein, high caloric diet.

LEWES, D.: *Mushroom poisoning due to amanita phalloides.* (Brit. Med. J., Aug. 21, 1948, 383-385).

Two German prisoners of war suffered poisoning from eating amanita phalloides, but both recovered. Elimination of the poison (amanita toxin) is accomplished by the gastro-intestinal tract aided by early and efficient gastric and colonic lavage. Atropine also was employed.

HOFFMAN, LT. COL. I. L.: *Spontaneous evacuation of metallic mercury from the vermiform appendix.* (Bull. U.S. Army Med. Dept., Oct. 1948, Vol. 8, No. 10, 802-803)

The case is reported of a male child of 3 who accidentally swallowed 4 c.c. of metallic mercury, and the course of the metal followed by serial X-ray studies of the abdomen. The mercury was first visualized in the appendix 24 hours after swallowing it. A film 5 days later indicated that the appendix had evacuated the mercury and 9 days later there was no metal in the gastrointestinal tract. Treatment consisted of a bland diet, mineral oil, no laxatives, an elevation of the foot of the bed at night. At no time were any symptoms of toxicity noted. In some similar incidents metallic mercury has caused inflammation of the vermiform appendix necessitating appendectomy. The accidental rupture of the terminal balloon of the Miller-Abbott tube may release the mercury by which it is weighted.

Obstructions of the alimentary tract. WILLIAM E. EVANS. (Radiology 51, 1, 23. July 1948).

The distribution of the more common obstructing or potentially obstructing lesions observed in 400 infants during the past seven years at Children's Hospital of Michigan is the following: Hypertrophic stenosis of the pylorus 50%, intussusception 20%, atresias of the esophagus 4%, atresias of the duodenum 2%, atresias of the jejunum-ileum 3%, atresias of the colon-rectum 2%, atresias of the anus 5%. Strangulated hernia 8%, meconium ileus 2%, congenital bands 2%, volvulus 2%, The age of the patient is often an important consideration in pediatric diagnosis, and this is particularly so in alimentary tract lesions. The atresias, meconium ileus, and most of the cases of volvulus are seen during the first days of life. Hypertrophic pyloric stenosis usually occurs between three and ten weeks of age. It will be noted that there is little over-lapping of these three groups. Meconium ileus is difficult to differentiate from ileal atresia, however, if there is no abrupt termination of the gas distended bowel, and if there is a mottled appearance of the meconium and a very small caliber of the colon, meconium ileus may be recognized. Good illustrations show the different pathological conditions.

Franz J. Lust

SEAGRAVE, KENNETH H.: *Kaposi's disease. Report of a case with unusual visceral manifestations.* (Radiology 51, 2, 248. August 1948.)

Kaposi's disease is an uncommon but interesting type of tumor, of low-grade malignancy, which may involve any part of the body. The growth is also called, more properly, multiple idiopathic hemorrhagic (pigmented) sarcoma. The cutaneous manifestations characteristically appear on the extremities as elevated vascular nodules which become pigmented. Visceral involvement is less frequent. In the described case, the initial growth was in the nasopharynx, followed by characteristic skin lesions and later by evidence of devastating gastrointestinal involvement. The roentgenological examination revealed intraluminal masses throughout the small intestine which proved to be polypoid growths of multiple hemorrhagic sarcoma.

Franz J. Lust

SHPINER, L. B.: *Erosion of the gastro-epiploic vein simulating an ulcer syndrome.* (Ill. Med. J., Feb. 1949, Vol. 95, No. 2).

A case is described in which a 38 year old man died from a hemorrhage occurring from an eroded vein in the upper greater curvature of the stomach, which was ligated at operation, death being due to the supervention of post-operative cardiovascular collapse. There was no aneurysm of the vessel and no mucosal scars to indicate previous gastric ulceration. A mild chronic gastritis was suggested by microscopic examination of the mucosa. He had had a history of episodes of hyperacidity responding to antacid treatment, and several G.I. X-ray series had been negative over a period of 5 years. He was a hyperkinetic individual given to anxiety because of his marginal economic status, and a year prior to his death a distressing family episode had produced ulcer symptoms, although no ulcer had been found. The bleeding from the eroded vein was voluminous and 12 pints of blood were used in transfusion. The author assumes that the chronic gastritis probably led to the erosion of the vein and the patient had had a previous severe hemorrhage from the stomach. He also predicates the hemorrhage on the autonomic nerve imbalance secondary to environmental stress. In the presence of local tissue anemia due to vascular spasm, a lowered resistance to the acid-pepsin factor could well account for the erosion.

THE PATHOLOGICAL PHYSIOLOGY OF OXALIC ACID IN MAN (OXALIC DIATHESIS). *By Joseph Khouri,* 120 pages, Masson et Cie, Paris, France, 400 Francs.

The author of this book has for 25 years been engaged in biological and biochemical research on oxalic acidemia, a disease peculiarly common in the Orient where he works. He is eminently qualified to his task of dealing with a problem which, in comparison with that of uric acid, has always been somewhat neglected. To facilitate an understanding of the subect, the work is divided into two principal divisions. The first deals with the general properties of oxalic acid, its origin, its formation in the living organism, the specific physico-chemical reactions to its toxicity, as well as the various quantitative technique for its estimation in the body. Selective procedures are described which approach the usual degree of accuracy of clinical biochemistry. All this prepares one for the second division which is exclusively devoted to clinical and therapeutic problems. The reader learns how to recognize and treat the condition in his current practice. Early diagnosis is essential, because delayed treatment, under some circumstances, leads to irreparable damage. This most interesting phase of pathology, so ably handled in this French text, will have a wide scientific appeal in general biology and to research students, as well.

WARD ADMINISTRATION AND CLINICAL TEACHING. *By Florence Meda Gipe, M.S., R.N. and Gladys Sellew, Ph.D., R.N.,* 357 pages. The C. V. Mosby Company, St. Louis, Mo., 1949, $4.25.

Since hospital administration cannot be efficient without good ward administration, the authors wisely focus their expert attention on plans for the ward in relation to the functions of the hospital and the control of nursing service. Both the personal and financial aspects of ward administration are thoroughly covered, including staff education for the general duty nurse. The intricacies involved in the efficient management of wards in large city hospitals are almost inconceivable, and it is doubtful if any single element in the machinery has been overlooked by the present authors. The book should prove invaluable to anyone actively interested in the administrative phases of hospital life. The authors refrain from giving advice on the selection of head nurses and refer this matter to the National League of Nursing Education.

NOVOCAIN INJECTIONS RELIEVE ARTHRITIS

A special 1:1000 solution of Novocain in graduated one liter administration flasks for use largely by intravenous injection in the treatment of arthritis and other conditions has been made available to physicians and hospitals by Winthrop-Stearns Inc., pharmaceutical manufacturer.

Intravenous therapy with Novocain solution to relieve pain and increase mobility in arthritis has been the subject of a number of recent medical publications. The special solution is also indicated for the treatment of sprains and fractures, puritus, serum sickness and post-operative pains, according to Dr. J. B. Rice, the company's director of medical research.

Published scientific papers reporting on well over 3,000 infusions state that this treatment may be administered by physicians through an easily acquired technique.

The new solution, developed through clinical research, is being produced at the Myerstown, Pa., plant of Winthrop-Stearns.

PHARMACISTS' STATUS TODAY INCREASES IN IMPORTANCE

Increasing importance of the pharmacist today as "a consultant to the physician, dentist and veterinarian" was recently emphasized by Charles F. Lanwermeyer, chief pharmacist, Abbott Laboratories, North Chicago, Ill., addressing the 51st annual convention, National Association of Retail Druggists.

More than a score of new products in eight different fields, unknown ten years ago, are now being sold through drug stores, Mr. Lanwermeyer pointed out. The eight fields mentioned were antibiotics, hormones, antimalarials, sulfa drugs, insecticides, hematics, cardiovascular drugs, antihistaminics, analgesics, and sedative hypnotics.

"In the field of strictly experimental drugs, those which are not ready for official recognition, we find new antirheumatics, muscle relaxants, and radio-active isotopes," he added.

"Accordingly the pharmacist is acquiring a higher place than ever before. He is now relieved of many of the mechanical manipulations of prescription dispensing and is taking his place as a consultant to the physician, dentist and veterinarian.

"Indirectly his standing as a professional man in the eyes of the public is also increasing. The public, as well as the physician, today looks to the pharmacist for information."

PRICE CUT ANNOUNCED ON PARENAMINE 6 PERCENT

A 40 per cent reduction on Parenamine 6 Per Cent, the "life-saving" protein hydrolysate for parenteral injection, was recently announced by Joseph G. Noh, vice-president, Winthrop-Stearns Inc.

The new price for a 1,000-liter administrative flask is $2.25, as compared with the former price of $3.75. The reduction, according to Mr. Noh, was made possible by increased production resulting from heavy demand for the new formula announced last February.

Distributed through physicians, hospitals, clinics, retail and wholesale druggists, Parenamine 6 Per Cent contains all the amino acids known to be essential to man, plus other amino acids native to casein. The new formula assures stability and purity of the product, which is described as "crystal clear, virtually salt free, allergen and pyrogen free."

Many lives once lost are today being saved by administration of this protein hydrolysate in the prevention and treatment of protein malnutrition. It is indicated for use in gastro-intestinal disturbances, febrile states, major surgery, hemorrhages, trauma, burns, cirrhosis and other liver conditions, and in debilitated conditions due to protein malnutrition.

CONTAINER STOCKS

Inventories of steel sheets for container manufacture in American Can Company plants will, in general, be adequate to meet customers' estimated needs unless the steel strike continues for an unprecedented period, Carl H. Black, president of the Company, said

Mr. Black said the Company hoped to accomplish the difficult operation of handling the "normal current needs" of customers despite the difficulty arising out of meeting with existing stocks, the thousands of individual specifications as to types, gauges and sizes of material. He said that in the event stocks run below full requirements of materials for any types of containers, the Company will follow its established policy of equitable allocation so as to minimize hardships arising out of shortages.

A threatened strike in twenty-six of the Company's plants employing members of the United Steelworkers of America (CIO) was averted on September thirtieth when a supplement to existing contracts was signed providing for a common contract expiration date of March 15, 1950, and agreement by the Company to set aside 6 cents per hour of regular time worked for a pension plan to be negotiated by a joint committee. No wage increases were granted. The Company had agreed in earlier negotiations to assume all costs of the group insurance plan to which employees had been contributing.

The setting aside of this fund was agreed upon after the Union, following the Steelworkers' policy line, refused the Company's offer to extend to hourly-rated employees the annuity plan now in effect for salaried people, maintained at a greater cost to the Company than is called for in the arrangement with the Steelworkers. This plan includes a contribution of about 20 per cent by employees.

"Subscribing to the principle that all employees should receive equal consideration in matters pertaining to social security," Mr. Black said, "we had been making preparations to offer the program to hourly-rated employees long before the current bargaining conferences. We discussed the plan with CIO officers last June, and it was offered in these negotiations. We strongly believe in the principle of contributory pension programs" he said, "and believe the regular Company annuity plan is in the best interest of all employees. Since by law, however, such benefits have become a subject for col-

The Cytologic Examination Of The Gastric Juice And Mucus

By

JOHN H. TOMENIUS
STOCKHOLM, SWEDEN

Attempts have long been made to draw conclusions from the microscopical appearance of the sediment of the gastric juice as to the pathological condition of the gastric mucous membrane. These earlier examinations however, have been of no great value, partly because the cytological findings were not correlated with reliable acidity and gastroscopical determinations and partly because methods employed in the cytological examination were vitiated by various sources of error. The examination of the secretion from the gastric mucous membrane has been and still is a difficult matter. If comparative estimations of secretions from the gastric mucous membrane are to be made, one must, as a first condition, see to it, that one receives these secretions as far as possible free from contaminations. In a digestive system, in which there are secretions both in the passages leading to the stomach and in those leading from it, the risk of cell contamination is very great. The problem in the author's investigations was this: Is it possible with an improved method in the cytological examination of the gastric juice or gastric mucus to obtain a correlation between, on the one hand, the cytological findings and on the other hand, the gastroscopical findings, the acidity and the secretory state respectively? The first task was to work out a method in which the chief sources of error were eliminated or controlled. In publications 1944-46 (Nord. Med. 1945: 26: 1015 ibid. 1945: 28: 2563 and Acta Med. Scand. 1946:

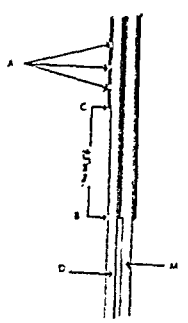


Fig. 1

123) the author described another difficulty met with in earlier examinations: the rapid destruction of the cells due to the action of acid or proteolytic ferments. To counteract this the author maintains a constant drip of sodium-bicarbonate solution in the stomach during the examination, which ensures a neutral or alkaline reaction in the stomach during the whole time of the examination. The tube used in the examinations has several different objects to which it must be adapted. Thus it must:

(1) Prevent or control contaminations from the upper digestive or respiratory passages.

(2) Prevent or control contaminations from the duodenum.

(3) Supply the neutralizing bicarbonate solution to the stomach.

(4) Suck up this solution and the secretion from the gastric mucous membrane.

To achieve these objects a tube has been constructed the upper and lower parts of which are illustrated in figs. 1 and 2.

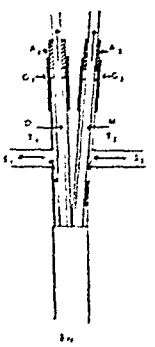


Fig. 2

The tube consists of an exterior thicker one, inside which there are two thinner interior tubes. One of these (D in fig. 1) is introduced into the duodenum, and the other (M in fig. 1) is intended to enter the stomach. The exterior tube, which has a number of large holes (M in fig. 1) in its lower part is pushed down to the cardia. In the correct position the tapshaped lower part (B-C) in fig. 1 terminates in the stomach but the holes A are in the oesophagus above the cardia. The bicarbonate solution runs from a drip arrangement (Fig. 3), and then through the sidearm S_2 on the T-tube T_2 fig. 2.

In the space between the gastric tube M and the exterior tube this bicarbonate solution runs down and emerges between the tapshaped part of the exterior tube and M (fig. 1). At A (fig. 1) mucus in the oesophagus is sucked up and carried via S_1 (fig. 2) to a bottle (fig. 4).

On this figure is also to be seen the arrangement for continous suction under constant negative pressure, which is controlled by a manometer. By means of a valve the negative pressure also can be controlled as desired. There are separate catchbottles for the mucus in the oesophagus, for the contents of the stomach and for the duodenal secretion. There is also a bottle for the saliva. In its lower part the gastric tube, M, has a number of holes to facilitate the suction. The olive has large longitudinal openings instead of holes, by which the sucking up of mucus is facilitated. The duodenal tube, D, is constructed according to Künztler (see Nord. Med. 1945: 28: 2563).

When the tube is applied both the duodenal and the gastric tubes are drawn into the exterior tube, which makes it considerably easier to introduce the tube. When the exterior tube reaches the neighbourhood of cardia (X-ray control) the duodenal tube is pushed down to the pylorus. The insertion is facilitated by a mandrin in the upper part of the duodenal tube (see Nord. Med. 1944: 23: 1757). The patient then lies on his right side until the tube has reached the duodenum, whereupon the gastric tube is introduced into the lower part of the stomach. Although the exterior tube is rather thick and experiments have lasted several hours, the patients have suffered no great inconvenience. On one occasion strong suction led to a coughing, which was probably caused by the suction in the lower part of the oesophagus. The method described has yielded a control of the contaminations. *By maintaining a neutral or slight alkaline reaction in the stomach, it is possible to differentiate the cytological picture, which previously has been able only in special cases.*

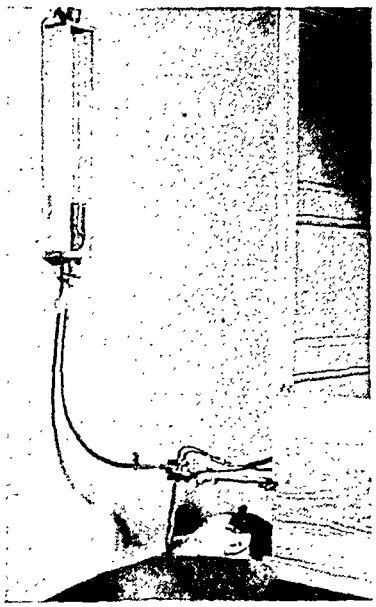


Fig. 3

The investigations which the author has made have clearly shown that the fasting juice is of slight importance for cytological purpose. As a rule it is impossible to differentiate the sediment. There has been no correlation with the gastroscopical picture or the acidity. In the examination described below therefore, the fasting juice was first brought up, and then the stomach was flushed clean with 300-500 ml. of water, 50 ml. at a time. Then a 1.3% solution of bicarbonate was allowed to drip into the stomach at a constant fixed rate. The contents of the stomach were sucked up in 10-minute periods during 90-120 min. test. Secretion stimulation was also given in the form of a subcutaneous injection of histamine. *It proved, that by the method described, a sediment which could be differentiated was secured* (Fig. 2).

Earlier investigations in this field have, owing to the destructive effect of HCl and ferment, only comprised examinations of cell remnants i.e. which remained when the gastric juice had exerted its peptic effect on cellular elements (See fig. 5).

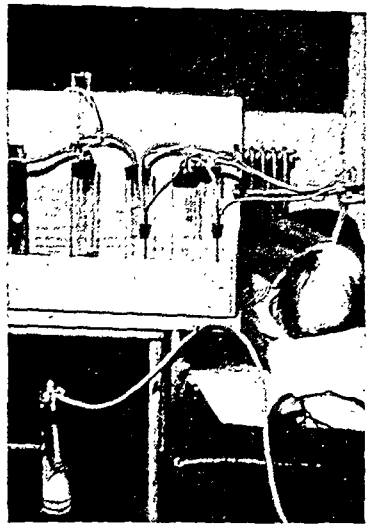


Fig. 4

But it is not only the acid gastric juice that destroys the cells, for the juice in the duodenum also has a similar property, which is evident from the author's experiments. Thus a digestion control, in which *the neutralized gastric juice* was allowed to act for a certain time at 37° C on white blood corpuscles was necessary. Only cases in which these were not destroyed were included. It was of importance that this source of error should be excluded in cases where no, or only a few cells were obtained. By means of this method an interesting correlation has been obtained between the cytological findings on the one hand and, on the other hand, the gastroscopical examination, the acidity and the gastric secretion respectively. Of course in all cases controls have been made of the sediments obtained from the contaminating digestive passages: the saliva of the mouth, the mucus in the oesophagus and the juice in the duodenum. Only in those cases where similar cells were not present to any considerable degree have been included. A moderate degree of contamination by squamous cells (certainly from the oesophagus) was met within the majority of the cases.

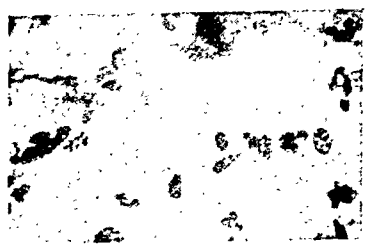


Fig. 5
Cell remnants, impossible to classificate. (From gastric residuum)

The author has examined material consisting of 72 cases. Of these 26 were normal and the rest comprised the commonest diseases in the stomach and duodenum

such as chronic gastritis, duodenal ulcers, gastric ulcers and cancers of the stomach. It was found that in normal cases there were only few cells in the sediment. Of these most were squamous cells (impurities from the mouth and oesophagus). Only 1.7% of the cells were leucocytes.

The cases of chronic gastritis fall into two groups, namely, (1) cases of current chronic gastritis with remaining acid secretion and 2) gastropathies with pale, atrophic mucous membrane without acid secretion. In the first group one found an average cell-density per visual field that considerably exceeded that of the normal cases. Most of the cells were leucocytes. In the second group with atrophic mucosa the cell picture resembled that of the normal cases.

In the group of duodenal ulcers one found the same picture as in the normal cases.

In the group of cancers of the stomach there was a very marked leucocytic picture. Red blood corpuscles were also richly represented.

In some cases of gastric ulcer without a surrounding gastritis the sediment was as in normal cases.

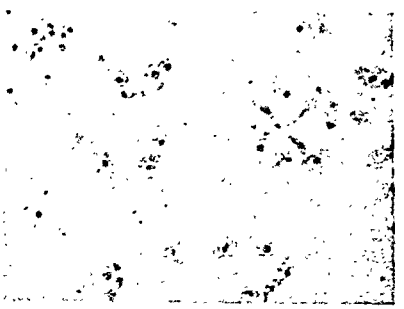


Fig. 6

Squamous cells (the author's method)

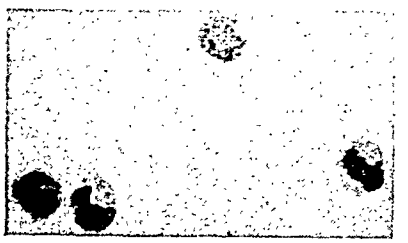


Fig. 7

Leukocytes (The author's method)

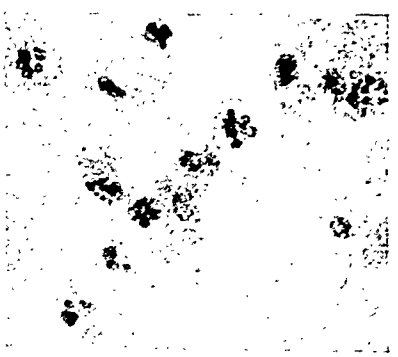


Fig. 8

Leukocytes with hypersegmentation (The author's method)

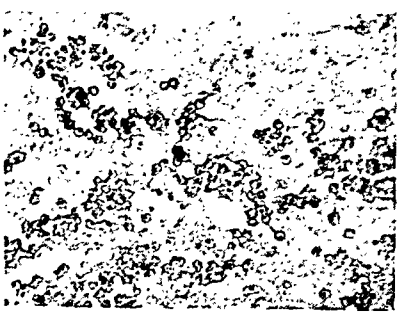


Fig. 9

Probably plasma cells (The author's method)

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Volume 16
Number 12

The Surgical Treatment Of Peptic Ulcer
Surgical Indications and Operative Procedure

By

WILLIAM P. KLEITSCH, M.D.

LINCOLN, NEBRASKA

The patient with a chronic peptic ulcer can be assured relief of symptoms in almost all cases if the right operation is done upon a properly selected patient. The relief of symptoms following adequate ulcer surgery is dramatic. The number of failures should be less than one percent and the mortality rate should be less than five percent. The morbidity is likewise low and the average postsurgical case is ready for discharge from the hospital between the seventh and fourteenth day. By this time he is ambulant and eating a regular diet although not in normal quantities.

The surgical cure of peptic ulcerations enjoys its greatest success when attempted on properly selected cases. The factors which suggest that a peptic ulcer can no longer be treated as a medical problem can be collected into two distinct groups. The following conditions can be considered to be *absolute indications* for surgery:

1. STENOSIS AND OBSTRUCTION due to edema and/or cicatricial contraction. This is reflected in advanced cases by postprandial left upper quadrant cramping and vomiting. Early cases are best demonstrated by x-ray; 50 percent retention of a barium meal six hours after ingestion being indication for surgical intervention.

Once obstructive symptoms have developed, surgery is indicated despite the fact that the obstruction can be relieved by medical treatment. The procedure of choice is to relieve the obstruction medically if possible, to restore the nutritional and electrolyte balance by a combination of oral and intravenous feedings and then operate for the obstruction when the patient is in an optimum physical condition.

2. SEVERE HEMORRHAGE. This is one of the most perplexing and serious of the complications incidental to peptic ulceration. The gravity of a serious hemorrhage lies in the fact that should uncontrollable bleeding develop, surgical intervention becomes a hazardous, if not fatal, procedure. It is, therefore, advisable in all cases which show a tendency to bleed, to consider surgery at an early date. We have set up an arbitrary rule of thumb to decide when bleeding cases become surgical cases. In patients over 40, one severe hemorrhage, and in patients under 40, two severe hemorrhages are sufficient indication for operative treatment of the ulcer. By severe hemorrhage we imply clinical evidence of bleeding, such as tarry stools, hematemesis and pallor, associated with laboratory findings of a lowered red cell count and hemoglobin.

3. PERFORATION. This is an acute emergency and in our opinion an indication for surgery in all cases. We feel that surgery is always indicated when a perforation of a peptic ulcer is diagnosed since the percentage of patients who die following perforation is much higher in the unoperated rather than the operated cases.

4. INTRACTABLE PAIN. This is produced by penetration of the ulcer into neighboring viscera. The head of the pancreas is the organ most frequently involved, although the gall bladder, liver and colon are sometimes involved. The prognosis for cure of a penetrating ulcer by medical management is poor and surgery will reduce the morbidity in these cases.

5. GASTRIC ULCER. Surgery is indicated for the treatment of gastric ulcer at an early date because of the danger of malignant degeneration. Patients over 40 in whom a gastric ulcer is demonstrated should be operated upon as soon as the preoperative preparation is completed. Patients under 40 should be treated medically, but if complete resolution of the ulcer is not demonstrable in three months, surgical resection is indicated. In addition to these absolute indications for gastric surgery there are several *possible indications* which may in certain cases, suggest that surgical relief is indicated.

1. INABILITY TO FOLLOW MEDICAL REGIME. There are certain people who, despite the best medical advice, are incapable of following the rigid therapeutic regime necessary for the medical treatment of peptic ulcers. There may be the question of financial ability. A patient may find it impossible from a financial angle to maintain an adequate diet and feeding schedule, and to supply himself with the necessary medications. More commonly one finds the type of work the patient does to be in conflict with a strict medical regime. Industrial workers and laborers who usually eat their noon meal from a mess kit, as well as traveling salesmen, bus drivers, etc., who eat the majority of their meals in restaurants, are often unwilling or unable to maintain the minimum dietary requirements. Finally, the patient may be of such a low order of intelligence that the necessary cooperation is impossible to obtain. In such cases surgical treatment of the ulcer may be advised.

2. ABDOMINAL SURGERY FOR ASSOCIATED CONDITIONS. It is sometimes discovered at laparotomy that an unsuspected peptic ulceration exists.

From the General Surgical Service of the Veterans Hospital, Lincoln, Nebraska.

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This occasionally arises during surgery on the biliary tract, ventral hernioplasty and exploratory laparotomy. If the abdomen is open the surgeon has an excellent opportunity to examine the lesion directly. If there are no other contraindications the ulcer may be treated at the time. We feel it is wiser, in the majority of cases, to do surgery for the ulcer at the time rather than subject the patient to another major operative procedure. We do not feel that surgery for peptic ulcers should be combined with surgery for perforated peptic ulcers. The reason for this is that perforation of a peptic ulcer is always associated with generalized peritonitis and the failure of suture lines is probably enhanced by the presence of this condition. It is our policy, therefore, to treat first the perforation and then, after all evidence of peritoneal irritation has subsided, to treat the ulcer.

3. CHRONICITY. The question of surgery for chronic peptic ulcers, with no indication other than chronicity, is probably a debatable point. It is our feeling that 18 months of medical management should be sufficient to indicate whether further relief is to be expected. If after this period of time symptoms are as bad or worse than when treatment was started, surgery should be recommended.

OPERATIVE PROCEDURES

After the decision is made that some type of surgical intervention is necessary for the treatment of a peptic ulcer, it then devolves upon the surgeon to decide which operation to choose to give the patient the greatest amount of relief. Many operative procedures have been described - - - many being merely technical variations of the same physiologic principles. We have felt that we have been able to resolve these principles to a relatively few procedures which can be applied to the treatment of ulcers as the individual case demands. The physiologic aim of surgery for peptic ulcers is to reduce gastric acidity and motility. Gastric acidity is reduced by resecting the acid-forming portion of the stomach, by neutralizing the gastric secretions with duodenal contents and by interruption of the nervous pathways which stimulate the secretory mechanism of the stomach. To achieve these ends we utilize the following procedures:

1. SUBTOTAL GASTRECTOMY. This is the procedure of choice in the treatment of chronic peptic ulcerations. It gives uniformly excellent results with a minimum of postoperative morbidity. It removes the acid-forming portion of the stomach and for added effectiveness introduces duodenal secretions into the remaining portion of the stomach as a neutralizing agent. In selected cases this operation can be combined with an infradiaphragmatic vagotomy, which completes the physiological potential of surgery. We do not recommend infradiaphragmatic vagotomy with subtotal gastrectomy for all cases. However, there are certain strong indications for supplemental vagotomy and these are:

1. If the resection is technically difficult, division of the vagus nerves permits a more adequate mobilization of the esophagus and gastric cardia, thereby facilitating a higher resection. This is particularly true in the pyknic type of habitus associated with the transverse or "steer horn" type of stomach.

2. If the psychosomatic component is pronounced, it is felt that vagotomy gives valuable supplementary effect to the resection. The exact evaluation of the severity of the psychosomatic component is difficult to define and is determined to a great degree by experience. The type of individual in whom a vagotomy as well as a resection is indicated is one who has what has been described as a "gastric personality." These people react to unpleasant situations with their stomach, the most common expression of this reaction being belching. We do vagotomies on all air-swallowers.

3. If at operation the ulcer is found to be acute, hyperemic and edematous, we feel that as complete an operation as possible is indicated and, therefore, in these cases too, we do a vagotomy.

2. GASTROJEJUNOSTOMY. This we consider to be a purely palliative procedure. In the light of our present knowledge, gastrojejunostomy cannot be considered adequate operative treatment of peptic ulceration. We, therefore, reserve this operation for cases of inoperable carcinoma of the stomach, or for inoperable conditions of the pancreas or retroperitoneal lymph nodes, which produce a duodenal obstruction. Gastrojejunostomy, plus infradiaphragmatic vagotomy, is indicated in certain selected cases where a subtotal gastrectomy is not advised. Such cases are relatively few, but it is well to know that a gastrojejunostomy plus infradiaphragmatic vagotomy will give rather adequate ulcer treatment without the additional time and trauma incidental to a resection.

3. VAGOTOMY ALONE. Infradiaphragmatic vagotomy is probably not a good procedure if used alone because of postoperative complications; the most annoying of these being obstructive symptoms. If a vagotomy alone is done, obstructive symptoms will develop in a large percentage of patients. Such cases can hardly be said to have benefited from surgery since they still are medical problems. For this reason we have abandoned this procedure; as well as the fact that in certain cases it is impossible to find and divide all the branches of the vagus nerve below the diaphragm. Transthoracic vagotomy is particularly indicated for stoma ulcer following resection. Since such ulcerations are not common this procedure likewise is not common. A transthoracic vagotomy alone is an ill-advised procedure because the patient and the surgeon lack the benefits derived from an abdominal exploration.

We have studied a group of 48 consecutive cases for whom gastric surgery was done. A duodenal ulcer was present in 36, a gastric ulcer in 5, operable carcinoma in 4 and a stoma ulcer in 3. The operative procedures used were subtotal gastrectomy 35, subtotal gastrectomy and infradiaphragmatic vagotomy 10, gastrojejunostomy and vagotomy 1 and infradiaphragmatic vagotomy alone in 2.

There were three postoperative deaths; one was due to coronary thrombosis, one died of a massive pulmonary embolism and one died of pancreatic necrosis of undetermined cause.

When these cases were grouped according to ages several interesting points come to light. The average age of the benign lesion was 47.5 years and of the malignant lesion 52.5 years. The average age of the operative fatality was 57.7 years. When the number of cases is broken up into decades, we discover that we did 4 operations on patients in the second decade, 6 operations on patients in the third decade, 7 operations on patients in the fourth decade, 22 operations on patients in the fifth decade and 2 operations on patients in the sixth decade. It therefore appears that the mortality in this type of surgery increases with age, and it is our feeling that this factor should be seriously considered in determining whether or not surgery is indicated in any particular patient. If the 22 cases that were operated upon in the fifth decade had, in fact, been operated upon in the fourth decade, it seems probable that the over-all mortality of this group would have been less.

A follow-up questionnaire was sent to those patients with benign lesions and 27 reported either by mail or in person, for interview and examination. The period of follow-up of these cases was up to 30 months, and we were extremely gratified to find that 24 of these patients reported complete relief of all ulcer symptoms. Only one patient of this group reported that his ulcer symptoms were not relieved. This happened to be one of the patients in whom an infradiaphragmatic vagotomy alone was done. Every one of the cases of resection had relief of ulcer symptoms. Two of the patients had died of other causes after leaving the hospital - - - one died in acute alcoholism; the cause of death in the other is not known.

A gain in weight was reported as being present in 13 of the 27 cases. This gain in weight varied from 2 to 30 pounds and averaged 11.8 pounds per patient. This is probably somewhat higher than reported by other groups but not unusually so. Postoperative gastrectomy patients do not gain much weight. However, only two of our group reported an actual weight loss. Diarrhea was present in eight cases. The diarrhea, however, is reported to be intermittent and frequently follows the ingestion of cold food or drink. There is reason to believe that diarrhea is associated with dietary indiscretions and these together probably play a part in the failure to gain weight.

SUMMARY

1. The factors which make the peptic ulcer patient a surgical problem are presented and discussed.

2. The operative procedures commonly used for the treatment of peptic ulcers are briefly described.

3. Subtotal gastrectomy with or without supplementary vagotomy is the procedure of choice for the surgical treatment of peptic ulcers.

4. A series of forty-eight cases of gastric surgery is reviewed. Follow-up studies are reported. Results following subtotal gastrectomy have been uniformly excellent.

Proctology And The General Practitioner

By
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INTRODUCTION

The general practitioner can add greatly to his range of services to the patient (and incidentally to his own income) by careful proctologic study of each case. Unfortunately most physicians dislike examining the anal and rectal regions. These are "dirty" regions. However, inasmuch as a very large percentage of malignancy develops in the rectum, and inasmuch as these cases are very often discovered upon simple digital examination, the importance of such examination becomes immediately evident.

The relationship between other benign rectal conditions such as hemorrhoids, fissures, fistulas and so forth and the development of malignancy is still under consideration. No final conclusion can yet be drawn. However, there can be no doubt that a chronic irritative process anywhere in the body should be removed. Thus, all such [illegible]gy in the ano-rectal region should be discovered [illegible]inated as early as possible.

The relationship between benign adenoma and malignancy is more clear-cut. There can be little question that most solitary polyps of the rectum, if allowed to remain sufficiently long, will ultimately become malignant. Thus, these lesions require immediate excision.

Benign pathology such as hemorrhoids, fissures, anal ulcers, cryptitis and papillitis, and so forth should be discovered as early as possible to prevent further extension, to relieve the patient of unnecessary suffering, and to avoid unnecessary complications.

Most of these conditions can be diagnosed by the general practitioner by simple inspection, a digital examination, and the use of a short proctoscope. Sigmoidoscopy does require special training, but is readily learned by any practitioner. However, most lesions of the ano-rectal region can be discovered by the short proctoscope. If bleeding is observed to be coming from a higher level, and the practitioner does not desire to perform a sigmoidoscopy, consultation with a proctologist is indicated.

The general practitioner bears the brunt of directing the patient properly. To him comes the ultimate credit if the patient is handled successfully, or the opprobrium if the patient is dissatisfied. The general practitioner must consider the economic aspects of consultation and surgery as well as the physical needs of the patient. Thus, whatever can be done to reduce the cost of proctologic care reflects itself to the credit of the family physician.

The techniques of ambulatory proctology provide an opportunity for a marked reduction in the cost of proctologic surgery. No hospitalization is required even if an extensive hemorrhoidectomy, prolapse or procidentia operation, fistulectomy or excision of pilonidal cyst, may be required. These operations are safely performed in a properly equipped office, and the patient is returned to economic usefulness within one or two days after surgery. Furthermore, there is no pain associated with surgery performed in this fashion. There is no pain with post-operative bowel movements. These patients are particularly grateful, and this gratitude reflects itself toward the general practitioner who refers the patient.

The average patient is fearful of rectal surgery. He is aware of the usual requirement of hospitalization and loss of time from work. He is further fearful of the traditional suffering that accompanies such surgery. If the general practitioner can assure the patient that he will not require hospitalization, that he will return to work within one or two days after operation, and that he will have little or no pain, this patient will not postpone necessary attention. Thus, many patients will be saved needless suffering, and occasionally an early malignancy or potentially malignant condition will be discovered and eradicated.

Indeed, the very act of examining the anal canal and rectum sets the examiner apart as ar unusual physician. The average examination unfortunately does not include inspection of these regions. Thus, if the general practitioner includes such study in his approach he will be considered unusual and exceptionally thorough by his patient. Proctologic study thus becomes extremely advantageous both to the patient and to the practitioner.

The scope of ambulatory techniques is not well understood by the average general practitioner. Inasmuch as the responsibility for early diagnosis and referral rests upon him it becomes the purpose of this paper to present the possibilities of this proctologic approach.

AMBULATORY PROCTOLOGY

I have previously defined ambulatory proctology in the text book of the same name as the diagnosis and treatment of diseases of the anus, rectum and sigmoid bowel without confining the patient to bed[1]. This treatment may be medical or surgical, conservative or radical. If the patient is not confined to bed that treatment is ambulatory. Thus, if a proctologist excises a pilonidal cyst, performs an extensive hemorrhoidectomy, or amputates a rectal prolapse, and then returns that patient to his home, although not necessarily to bed, that case has been treated by ambulatory proctology.

The very limited interpretation of ambulatory proctology that considers it to be synonymous with the injection treatment of hemorrhoids is entirely erroneous. Indeed, if the proctologist's office is well equipped, with operating table, sterilizers and autoclaves, complete surgical instrument sets, appropriate anesthetic apparatus, and adequate assistance, that office is actually an operating room. Under these circumstances all proctologic procedures can be performed with complete safety to the patient.

These patients may, without undue risk, leave the office after operation. They often drive their own car home.

This concept is not radical. It is merely a logical interpretation of the term ambulatory proctology. Ambulatory proctology is not injection therapy. The injection treatment of hemorrhoids does have merit in selected cases. However, surgery is more often indicated. Injection therapy should not be used in those cases where surgery is indicated. It thus becomes evident that ambulatory proctology offers exactly the same techniques as are available to the hospital patient. The only important differences are first, the patient's comfort is a primary consideration (oil soluble anesthetics and the like), and second, the patient is not hospitalized. The techniques of therapy, both surgical and non-surgical, are otherwise exactly similar to those employed in hospital proctology. Thus, any procedure employed in ambulatory practice may be utilized in hospital cases. The scope of ambulatory proctology may be generally indicated by listing the pathology that indicates proctologic study. This list would be as follows:

1, Pediatric proctology pathology—fissure, polyp, prolapse, megacolon, etc.; 2, Pruritus ani; 3, Cryptitis and papillitis; 4, Anorectal fistula; 5, Perianal and perirectal abscesses and infections; 6, Anal ulcer; 7, Hemorrhoids; 8, Prolapse and procidentia; 9, Enterocolitis and colitis; 10, Ulcerative colitis; 11, Bacillary dysentery; 12, Tuberculosis; 13, Lymphogranuloma venereum; 14, Venereal diseases; 15, Intestinal parasites; 16, Constipation; 17, Melanosis Coli; 18, Diverticulosis and diverticulitis; 19, Benign tumors; 20, Multiple adenoma; 21, Malignant neoplasm; 22, Pilonidal dimple, sinus, cyst, and abscess; 23, Coccygodynia; 24, Rectal stricture and anal stenosis; 25, Anal incontinence; 26, Foreign bodies and rectal trauma.

This list of proctologic pathology indicates in a general fashion the scope of ambulatory proctology. One further category should be added - - - psychosomatic proctology. There is a strong psychosomatic background for many types of proctologic pathology. Mucous colitis is particularly illustrative of such pathology. Some proctologists feel that many cases of ulcerative colitis are psychosomatic in origin.

The scope of ambulatory proctology is so extensive that close cooperation is required between the referring physician and the proctologist. In my own practice of proctology all patients are referred. Thus, it is to the patient's best advantage if there is close cooperation between the general practitioner and the proctologist. Patients must be treated as a whole. The limited viewpoint of any specialist is often advantageous. However, it has its disadvantages. One of these disadvantages is that the patient is often considered as isolated pathology and not as an individual. The proctologist must not treat a disembodied rectum or colon. He must see the individual patient in his entirety, as a human being. Only under these circumstances, and this is best accomplished with the cooperation of the referring general physician, can the patient obtain the very best care.

INDICATIONS FOR PROCTOLOGIC CONSULTATION

Proctologic consultation is indicated in all cases where the referring physician is not properly equipped for proper diagnostic study. Thus, if the patient presents himself for a complete physical examination, and the general practitioner does not desire to perform a sigmoidoscopy, that patient's examination should be considered incomplete until sigmoidoscopy is performed. Thus, it is entirely safe to say that every patient who consults the general practitioner should either be sigmoidoscoped or referred to the proctologist. When the patient is made to realize that this is a concealed area, and that malignancy may be present without symptoms, he will immediately appreciate the value of such study. He will also appreciate the thorough nature of the general practitioner, and his concern for the patient's welfare.

When a patient presents symptoms related to the colon, rectum or anus or the perianal area, and the physician is not equipped for proper examination, consultation is again indicated. If the physician is equipped for such study, and the diagnosis is not immediately evident after study, consultation is required. If proctoscopic examination reveals the source of rectal bleeding to be hemorrhoids, sigmoidoscopy should still be performed. This is important because the patient may have pathology at a higher level as well, possibly an early or advanced malignancy. Thus, the obvious diagnosis must not be accepted at once. It is essential that study be completed before any diagnosis is made.

The major indications for consultation in symptomatic cases are bleeding, pain, protrusion, discharge, pruritus ani, constipation or diarrhea. An unaccounted for anemia is a further indication. Thus, it will be the rare patient who does not require careful proctologic study. This study may be performed by the general practitioner if he is properly equipped. If the equipment (or inclination) is not available, the proctologist must be consulted.

INSTRUMENTS REQUIRED

The general practitioner can perform an adequate examination with very few instruments. His most important instruments are his eyes and hands for inspection and digital examination. Beyond that a simple proctoscope will suffice for preliminary study. Sigmoidoscopy will be indicated in many cases. However, the average general practitioner may not desire to perform such examination.

It is indeed true that a table permitting inversion of the patient simplifies such study. Such equipment is often essential to facilitate proper sigmoidoscopic examination. If the general practitioner does not wish to so equip his office the proctologist should be consulted.

Any of the standard proctoscopes and sigmoidoscopes are useful. It is probably best to use a proximal-light type of sigmoidoscope. The distal-light instruments may present a confusing picture, and the bulb is often obscured by feces, mucus or blood. Thus, technical difficulties may result in missing the diagnosis when a distal-lighted instrument is employed.

Of the simple proctoscopes a tubular instrument without slot is preferable. An anoscope should also be part of the physician's equipment. The Hirschman anoscope is particularly suitable.

Highly specialized instruments such as my own sigmoidoscopes are not suitable for the general practitioner[2,3,4]. Indeed, even the proctologist will find it difficult to employ these instruments unless his office is equipped with special plumbing connections. However, these latter instruments are not always necessary. In most cases the diagnosis is readily made by routine examinations.

A biopsy punch is useful but expensive. Further, it is probably best to consult the proctologist when biopsy is required. X-ray apparatus is valuable for barium colon enema studies. If the general practitioner does not feel qualified for such study, it should be referred to the roentgenologist or the proctologist who is properly equipped.

No other equipment is necessary for examination by the general practitioner. Careful inspection of the sacrococcygeal area and the perianal area, digital examination of the anal canal, proctoscopy and sometimes sigmoidoscopy, constitute an entirely adequate examination in most cases. If further study is required the proctologist should be consulted.

THERAPY AND THE GENERAL PRACTITIONER

All non-surgical proctologic therapy may be safely handled by the general practitioner. Indeed, when the patient does not require surgery it is always my practice to refer him back to the general practitioner for necessary treatment. Indeed, even if surgery is indicated, and if the general practitioner is so inclined, he may assist at operation and be entrusted with the major share of post-operative management.

The early stages of pruritus ani, once an adequate diagnosis is made, can be properly treated by the general practitioner. Chronic, resistant cases are best referred to

the proctologist. Tattoo-neurotomy will be necessary in most such cases.[5 6 7 8 9 10]

Early cryptitis is readily treated by the general practitioner. However, an adequate diagnosis must first be made. If surgery is indicated the general practitioner will usually prefer referral to the proctologist.

Ano-rectal fistula does not fall within the domain of the general physician. In practically all such cases surgery is indicated. The perianal and perirectal abscesses and infections that result in such fistula also require specialized attention. It seems a simple matter to open such abscesses. However, unless the incision is properly placed subsequent fistula surgery becomes unnecessarily complicated. Thus, inasmuch as the proctologist will be required when the fistula develops, it is probably best to permit him the opportunity to incise and drain the initiating abscess.

Anal fissures are readily treated by the general practitioner. However, once the chronic ulcer has become established, surgery is indicated.

Internal hemorrhoids, when bleeding is the major indication for treatment, may be treated by injection therapy. This may be performed by the general practitioner if he is so inclined. When the hemorrhoids become complicated by prolapse or thrombosis, or in any other fashion, consultation is necessary.

Prolapse may occasionally be treated safely by injection therapy. However, most cases require surgery. Thus, consultation will again be indicated.

Colitis is often difficult to classify. However, once diagnostic study is completed, and classification is accurate, therapy may be entrusted to the referring physician. In all cases it has been my practice to return the patient to the referring physician together with a report of the complete diagnostic study, and a complete outline for subsequent therapy. These patients often have a strong emotional background. The family doctor is in an excellent position to understand this background, and to provide the proper therapy.

Lymphogranuloma venereum is infrequent in private practice. These cases are best treated by the proctologist. However, the picture is rapidly changing with the development of the newer antibiotics. It may well be that antibiotic therapy (aureomycin) will bring lymphogranuloma venereum within the range of the general practitioner.

The other venereal diseases involving the rectum and anus require careful diagnostic study. Once the diagnosis is established therapy is readily managed by the general physician.

Intestinal parasites merely require adequate diagnosis. Beyond that point the referring physician usually requires no consultation.

Constipation and diarrhea are often indications for consultation and complete proctologic study. However, if the study reveals no need for surgical therapy, the therapeutic management may be returned to the referring physician.

When a diagnosis of benign tumor or malignant neoplasm has been made the referring physician will usually prefer further management to be in the hands of the proctologist.

Pilonidal dimple, sinus, cyst or abscess are best left with the proctologist. These are surgical conditions.

Most cases of coccygodynia require careful study. Once the diagnosis has been established general medical management may be entirely adequate. If surgery is indicated the proctologist should be consulted.

Rectal stricture and anal stenosis are problems for the proctologist. The same may be said for anal incontinence, and most cases of foreign bodies in the rectum.

Thus, either alone or in cooperation with the proctologist, the general practitioner finds an extensive field of action in proctology.

CONCLUSIONS

Proctology, (particularly ambulatory proctology), has much to offer the general practitioner and his patients. Study of the anus, rectum and sigmoid is indicated in all general physical examinations. Both benign and malignant pathology will be discovered in early stages if such examination is routine.

The techniques of ambulatory proctology may be employed by the general practitioner in many cases. Whether in the hands of the general practitioner or the proctologist these techniques avoid hospitalization and loss of time from work. Thus, necessary treatment and surgery will not be postponed on an economic basis.

Rectal surgery, properly performed, is free from pain not only during, but after operation. These patients are especially grateful both to the general practitioner and the proctologist.

The scope of ambulatory proctology is defined, and is found to include all pathology of the anus, rectum and sigmoid and pilonidal disease. The simple instruments required for proctologic study are described.

Indications for proctologic consultation are detailed. These indications are seen in both symptomatic and asymptomatic patients.

The role of the general practitioner in proctologic therapy is described. Many proctologic conditions can be treated by the general practitioner alone or in conjunction with the consultant.

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Hyperplasia Of The Regional Lymph Nodes In A Meckel's Diverticulum With Ulcerated Aberrant Gastric Mucosa

By

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INTRODUCTION

A Meckel's diverticulum is derived from the emphalomesenteric or vitelline duct which is an anlage of early fetal life. Gray[1] states that it disappears at the seventh week of embryonic existence but in about three percent of cases its proximal part persists as a diverticulum. The Meckel's diverticulum results when the distal end closes and the ileal end remains open. It is located usually one to three feet proximal to the ileocecal valve and on the anti-mesenteric border. In Meckel's diverticulum there may be gastric mucosa, duodenal mucosa, jejunal mucosa, or pancreatic mucosa. These tissues may give complications which one finds in the Meckel's diverticulum.

The first case of gastric mucosa in a Meckel's diverticulum was reported by Denecke.[2] This was recorded in 1902. Deetz[3], five years later, pointed out the occurrence of gastric mucosa and stressed the peptic character of ulcer in Meckel's diverticulum. Lindau and Wulff[4] called attention to the secretion of hydrochloric acid in the gastric mucosa in a Meckel's diverticulum and they also pointed out the fact that the hydrochloric acid secretion occurs simultaneously with the same activity of the stomach.

REPORT OF A CASE

J. D., a boy, age sixteen, was seen July 30, 1945, with a history of three months previous severe pain in his abdomen, loc l zed around the umbilcus. The pain was a twisting type, spasmodic in nature, severe in character. It would occur about four hours after eating and sometimes earlier—to within an hour. Food sometimes relieved and occasionally did not relieve the pain. If the pain became very severe the patient was nauseated and vomited profusely. This pain would last anywhere from a half to four hours—at times so severe that the patient would lie on his abdomen and put his hands to the area of the umbilicus with a firm pressure, which gave some relief. These attacks became more frequent and severe. The patient lost weight—from one hundred thirty pounds down to eighty-four. Before this patient was seen—in another clinic, an appendectomy was performed through a small McBurney incision with probably no exploration, because the Meckel's diverticulum was not found and the patient's symptoms were not relieved.

Medication, like anti-spasmodics or ulcer alkaline therapy or ulcer diet did not help. The attacks became more frequent.

DIAGNOSTIC PROCEDURE

Gastro-intestinal study showed the esophagus was normal, the stomach of a fish hook type. The cap visualized with difficulty but finally appeared normal, there being a fairly marked amount of spasm present. The first and second portions of the duodenum were enlarged, showing early mesenteric ileus. In two hours the stomach was three-fourths empty and the small intestine was dilated showing a mucosal pattern typical of a disturbed motility of the small intestine.

In five hours there was observed a small area of barium which was considered to be Meckel's diverticulum, shown in Figure I.

(From the Surgical Service of Woman's Hospital, Cleveland, Ohio)
Submitted December 23, 1948.



FIGURE I

Gastric analysis showed in two hours' fractional analysis a low normal acidity. (Figure II).

GASTRIC ANALYSIS

Date 7-31-45											
Histamin											
Alcohol	60	cc									
Hour	Fast	15	30	45	60	75	90	105	120	135	
Free HCl	22	12	24	34	30	26	26	20	32	30	
Total Ac	50	22	34	54	46	48	40	34	58	56	
Mucus											
Bile									3+		
Blood							by test sl				
Fast 38 cc											

FIGURE II

Operative procedure was advised because medication gave no relief. The patient was operated under continuous fractional spinal anesthesia. An eight-inch right peri-rectus incision was made. The abdomen was explored thoroughly. It was found that the second portion of the duodenum was moderately dilated, confirming the diagnosis of a mesenteric ileus. The right ascending colon mesentery attachments were almost absent, resulting in a mobile cecum. Further exploration showed a Meckel's diverticulum two feet proximal to the cecum. It was delivered from the abdomen and

the intestine further explored. The obvious picture was the mesenteric leaf of the small intestine with its lymphatic distribution from the Meckel's diverticulum to the cecum showing a large number of firm lymph nodes ranging up to one centimeter in diameter. They were firm to palpation. They were also present in the lymphatic distribution on the Meckel's diverticulum. These were observed even previous to the finding of the Meckel's diverticulum. This was so characteristic when the cecum was brought into the operative field that at once a lesion was suspected in the small intestines because of the character and localization of the lymph nodes.

The Meckel's diverticulum was brought forward and the tip of it was an enlarged firm hard area with the characteristic feel of an intra-ulcer lesion. The Meckel's diverticulum and a small portion of small intestine were resected and a lateral anastomosis was performed by the usual interrupted silk technique with an opening two inches in length. The abdomen was closed in the usual manner. A small catheter drain was inserted to drain the peritoneal cavity. The patient made an uneventful recovery and has regained his normal weight, remaining symptom free.

PATHOLOGICAL REPORT BY DOCTOR SIMON KOLETSKY, PATHOLOGIST

GROSS: Pathological Description Specimen consists of

(a) A short segment of small intestine, (ileum), 4 cm. in length and 3.5 cm. in circumference, containing a Meckel's diverticulum. The latter arises from the free or anti-mesenteric portion of bowel, is 5 cm. in length and 3 cm. in circumference. The proximal 3 cm. of mucosa is grayish-pink, intact and resembles that of small bowel. In the distal two cm., the mucosa is thick, has a mosaic contour and is covered by a thin layer of mucinous fluid giving an acid reaction to Congo Red indicator. Near the tip is a deep, round, sharply defined, penetrating ulcer, 8 mm. in diameter with firm, nodular, brownish-red base, sharply defined edges and a pale white, cross-section which appears to penetrate through the muscular coat.

(b) A round nodule, 1 cm. in diameter, the outer aspect of which is covered by a thin, intact, gray fibrous capsule. Cross-section reveals an architectural pattern suggestive of lymph nodes. Cortex and medullary portions are preserved. The cut surface is soft to moderately firm, pale gray and homogeneous.

MICROSCOPIC: Figure III shows photomicrographic picture of ectopic gastric mucosa and ulcer area in Meckel's diverticulum.

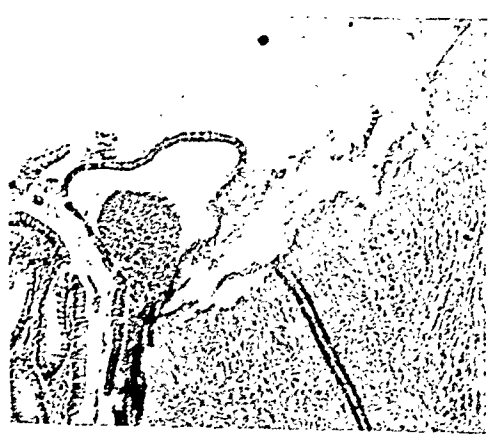


FIGURE III

MICROSCOPIC DESCRIPTION

(a) The ulcer extends to serosa with obliteration of the usual layers of intestine. The base shows a superficial necrotic layer infiltrated with polymorphonuclear leukocytes and lymphocytes and beneath this there is a mass of granulation tissue, richly vascularized with capillaries and also infiltrated with lymphoid cells and polymorphonuclear leukocytes. At the base there is a denser layer of moderately cellular, collagenous stroma. No indication of neoplastic change is found. There are regions of active fibroblastic proliferation. The mucosa at the edge of the ulcer is of both, small bowel and gastric type. In the latter there are numerous typical, closely approximated small tubules of the fundal type, containing both chief and also parietal or acid cells.

PHOTOMICROGRAPHIC PICTURE OF THE LYMPH NODE

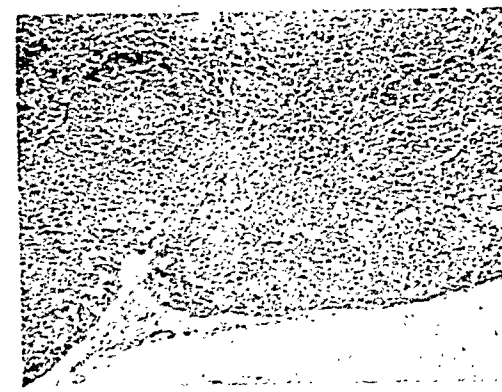


FIGURE IV

(b) The nodule shows the structure of lymph node with preservation of the usual architectural pattern. In cortex are numerous large follicles with hyperplastic secondary centers composed of immature lymphoid cells. The follicles are separated by diffuse masses of mature lymphocytes supported by a delicate reticular stroma showing focal reticular cell hyperplasia, also considerable edema and hyperemia. The capsule of the node is intact and shows focal exudation of mature lymphoid cells.

DIAGNOSIS: Acute and chronic ulcer of Meckel's diverticulum of ileum. Heterotopic gastric mucosa of Meckel's diverticulum. Lymph node, (mesenteric) the seat of hyperplasia.

A second case of Meckel's diverticulum was found in a patient, V. K., age twenty, operated on for pelvic pathology. An exploration showed that there was a Meckel's diverticulum measuring 9 cm. long by 1 cm. in diameter, with no evidence of any thickening suggestive of any aberrant mucosal changes. Exploration showed no enlargement of any lymph nodes in the mesenteric lympatic distribution of this Meckel's diverticulum.

Pathological findings of the Meckel's diverticulum showed no abnormal changes in the diverticulum. It was removed because of the fact that it was long and constricted at the neck where it entered the small intestine.

Three other cases of Meckel's diverticulum have been found incidental in laparotomy for other conditions—with no enlargement of the glands in the mesenteric leaf of lymphatic distribution of Meckel's diverticulum.

These five cases prove that incidental Meckel's diverticulum with no infection or aberrant or gastric or pancreatic mucosa does not give enlarged mesenteric lymph nodes.

DISCUSSION

The literature was searched for a picture of hyperplasia of lymph node in ectopic or aberrant gastric mucosa in Meckel's diverticulum. We were unable to find a description of the pathological hyperplasia of the lymph nodes which was observed in this case. We feel that probably this is a very important point in operations such as recurrent interval appendicitis because if the enlarged nodes occur in the mesentery leaf of the small bowel when appendix is delivered it is imperative that further exploration be done to make sure that one is not dealing with a Meckel's diverticulum with aberrant or ectopic gastric mucosa in Meckel's diverticulum.

CONCLUSIONS

1. Meckel's diverticulum with gastric mucosa with ulcer excreting acid was described in which the regional lymph nodes showed hyperplasia due to the ulcer in the aberrant gastric mucosa in the Meckel's diverticulum.

2. The importance of further exploration of the abdomen is emphasized when an interval appendix operation is being performed through a small incision, or in

exploration of the abdomen for obscure pain in the right lower quadrant. In such cases, if the regional lymph nodes in the small intestines proximal to the colon show lymphatic hyperplasia a search for a Meckel's diverticulum with aberrant gastric mucosa should be done.

3. We feel this lymph node hyperplasia has not been emphasized sufficiently in previous papers on Meckel's diverticulum with ectopic gastric mucosa or pancreatic tissue to alert one to the significance of these findings.

4. Hyperplasia of the regional lymph nodes in a Meckel's diverticulum with ulcerated aberrant gastric mucosa is found only when a Meckel's diverticulum has a complication of aberrant or gastric mucosa. This is proved by the report of five cases of Meckel's diverticulum.

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Effects Of Malnutrition Upon Mothers And Infants In Naples 1945

By

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During the summer of 1943 a plan was evolved by the Service Committee of the American Unitarian Association to combine relief feeding of some portion of war-devastated Europe with the scientific study of nutritional problems. In January of 1944 the Service Committee of the Congregational Christian Churches offered to share in this program, thereby making a more comprehensive program and a larger team possible. Deliberate selection of personnel and equipment was undertaken by joint chairmen (E. L. Sevringhaus and M. B. Visscher). The United Nations Relief and Rehabilitation Administration requested the team to carry out its program under the joint sponsorship of U. N. R. R. A. and the Service Committees, both of the American Unitarian Associations, and of the Congregational Christian Churches as a "non-reimbursable loan" from the latter groups. This arrangement afforded not only official permission to enter an area, but also provided transportation and subsistence costs for part of the personnel, and much of the bulk food of staple types. Since the first area open for such work was Italy, the members of the team began to reach this country in April, 1945. The organization plan provided for two teams working simultaneously, one conducting a series of spot surveys while the other made detailed studies in one city on correlations between the nutritional status and health both before and after relief feeding.

Italian nationals who were employed as associates included physicians, nurses, medical students, and clerical workers. In conference with Dr. Roy Butler, Dr. A. J. MacQueeny and Dr. J. Metcoff of the UNRRA staff, the code system of signs and symptoms of nutritional deficiencies designed by Dr. A. Hughes Bryan for international use by UNRRA teams, was expanded, and definitions of the terms agreed upon. Drs. MacQueeny and Metcoff also participated in training Italian examiners for the work. A mobile team operating, at first under the direction of Dr. E. L. Stebbins, and later under Dr. James Perkins, made observations in eight different communities from north to south, both devastated and undamaged. Their observations will be reported separately elsewhere. One feature of the work of their team was the examination of 19,271 chests with a portable photofluorographic X-ray unit loaned by the U. S. Public Health Service. This survey showed the incidence of tuberculosis to be from 0.7 to 3.7 per cent in the areas studied and in one area of Naples they found an incidence of 6 per cent. It was also apparent that the incidence of typhoid, malaria and diphtheria was increased. Blood smears used as a diagnosis for malaria revealed wide differences between communities. The special dental aspects of this survey study have been published in part (1). The incidence of frank vitamin deficiency diseases was low, as has already been reported for some parts of Italy by MacQueeny and Metcoff (2). Acute and old rickets were extremely frequent, in agreement with the report of these authors.

During the initiation of this survey program it became apparent that an exceptional opportunity for the intensive study of the results of supplementary feeding existed at the Medical School of the University of Naples. In the immediately adjacent buildings of the three departments necessary to the proper conduct of the study, (i. e. dental, pediatric, and obstetric and gynecology) and with the cordial cooperation of Prof. Auricchio (Pediatrics), Prof. Giardino (Dentistry) and Prof. Tesauro (Obstetrics and Gynecology), the eight American members of the team, under the direction of Dr. Sevringhaus, employed ten Italian physicians, two nurses and several clerical assistants and interpreters. The equipment still available in the Italian hospitals combined with that purposely provided by the team made possible some of the laboratory procedures which were essential to the assay of nutritional deficiency states and to the detection of diseases as well as the customary case histories and physical examinations. Arrangements were made to provide an Italian baker with wheat flour, to which various adjuvants, such as soya flour, wheat or corn germ, or sun-flower seed flour, had been added, thus loaves of bread using this flour were obtained and supervised food distribution was undertaken. Similarly these blended

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flours were made up by an Italian mill into the convential "pasta" forms. These materials together with powdered whole milk, powdered skim milk, cane sugar, dried beans and peas, and small amounts of canned fish, lard, and cocoa powder, provided by UNRRA, formed the food supplies issued to patients accepted for the study. The recipients were limited to children and women, because of the terms of the agreement covering UNRRA assistance to Italy. The special problems to be reported include nutritional and general health status of pregnant women and of teen age girls in 1945. A report on some problems of infant nutrition has been made by Dr. Frank Gollan (3). Reports of other phases of the work of the Italian Medical Nutrition Mission will subsequently appear.

PREGNANCY STUDIES

Examinations and observations on approximately 200 pregnant women were obtained in the I. M. N. M. clinic in the period from July through December 1945. These women were, for the most part, prenatal outpatients from the Hospital's Obstetric Service. A small number came as referrals from the Naples UNRRA (welfare) staff and other sources. It was planned that the subjects selected should be in the last trimester of pregnancy and that no food supplements other than vitamins and iron salts would be given until after delivery. Observations on mothers and babies were designed for use in evaluating the nutritional status and effect of the mother's diet on pregnancy, labor and the off-spring. Data quoted relative to the mothers were obtained at the first examination, before any diet supplementation was supplied.

Since we could find no comparable earlier studies reported in the Italian literature it was necessary to compile such summaries as were possible from the hospital records in order to have data on pre-war nutritional status and general health for purposes of reference and comparison. Since the translation into English terms and the tabulation of data from the Hospital record sheets was a time consuming task it was necessary to choose certain time periods which would reflect the contrasts in food supply and therefore general nutrition. The dates chozen as representing, according to resident Italian doctors, typical periods were 1939, pre-war nutrition; 1944, year of most severe food shortages; and 1945, increased food consumption because of available American military and UNRRA supplies.

SELECTION OF CLINICAL MATERIAL

No difficulty was encountered in obtaining a sufficient number of subjects to fill in the series of the desired size since the outpatient group and those patients referred by others brought new subjects as rapidly as they could be handled.

The patient's history was obtained on her first visit by one of the interpreter staff who had been trained by us to assist with the medical records. The dietary history included information on the number of times per week that meat, fish, cheese, eggs, milk, and fresh fruit were eaten. The economic status was judged on the basis of the daily income, the amount spent for food, current food prices, and the number of persons fed. It was noted how long the economic level present at the time of examination had been maintained at that level and how the present diet differed from the former. In taking the case histories, attention was also paid to the possible influence of wartime conditions on the incidence of diseases, ordinarily considered prevalent in that region, and the bearing that these findings might have on the nutrition of the individual. The number of pregnancies, the complications thereof and number of living children were carefully checked; these data and pertinent observations will be published separately by Dr. L. W. Sontag.

METHODS OF EXAMINATIONS

The physical examinations were complete except for pelvic and rectal examinations which were done routinely in the regular prenatal clinic. All items included in the code system of signs and symptoms of nutritional deficiencies, previously mentioned, were checked and, in addition, a number of anthropometric measurements were routinely made. Some of the group were examined in the I. M. N. M. dental clinic and most of them were examined by fluoroscopy.

The laboratory work originally planned could not be completed on all subjects but one or more hemoglobin determinations and red blood cell counts as well as urinalysis and blood Wassermann tests were done on nearly all of the patients. Blood determinations of vitamin A and carotene, vitamin C and serum protein were done in a fair proportion of cases. There were also a number of stool examinations for parasites made in this group.

The pregnant women were seen at intervals up to the time of delivery. Observations during hospitalization were made by Dr. Vaglio since he was one of the hospital staff physicians who had been assigned to the I. M. N. M. team. Fairly complete labor records and laboratory data were thus obtained as well as follow-up reports on both mother and infant. It was usually possible to obtain weights and measurements on infants but only a few of the much desired X-rays of bone development could be made because of the electric power failures and other shortcomings which rendered the X-ray facilities inadequate.

TABLE 1

Number of Pregnancies and Incidence of Complications of the Clinica Ostetrica, Naples

	1939		1944		1945	
	Cases	per cent	Cases	per cent	Cases	per cent
Total pregnancies	550	100	267	100	680	100
Full term deliveries	427	77.6	169	63.3	456	67.1
Abortions	123	22.4	97	36.3	217	31.9
Extra-uterine pregnancies	0		1		7	1.0
Toxemias	2	0.3	1	0.4	9	1.3
Complications at delivery	94	17.1	94	35.2	155	22.8
Other complications of pregnancy	53	9.6	32	12.0	212	31.2
Total complications	149	27.1	127	47.6	376	55.3

OBSERVATIONS

The data on pregnancies and complications (Table 1) are based entirely upon the diagnostic groupings of the Italian staff of the Clinica Ostetrica. This was done so that uniform standards between the years 1939 and 1945 would be assured. The women in this group were all delivered in the hospital and whatever abortions occurred took place in the hospital, and the Italian staff considered that these abortions were essentially spontaneous. Non-therapeutic induced abortion seems to be an infrequent problem in this hospital. It is, therefore, considered to be significant that the proportion of pregnancies which terminated in abortion was definitely increased during 1944, the year of greatest dietary stringency, and that there was some decrease in their number at once in the next year.

The toxemias which were relatively infrequent, became more numerous soon after the food supply was improved. This has been observed in other studies (4) (5) (6). The striking increases in the various complications of pregnancy and of delivery in the later years undoubtedly must be related to the increased incidence of various infectious illnesses as well as with the nutritional status *per se*.

TABLE 2

Number of Babies Born at the Clinica Obstetrica, Naples

	1939	1944	1945
Totals	435	174	471
Males	227	100	254
Females	218	74	217
Stillbirths	54 (12.4%)	23 (13.2%)	80 (17.2%)
Males	30	15	45
Females	24	8	35
Twins	8	5	15
Males	5	3	4
Females	1	1	7

The decrease in the number of pregnancies (Table 1) and in the number of babies born (Table 2) in 1944 is to be expected as the result of disrupted family life, absence of most Italian men in military service before the Allied forces entered Italy in the latter half of 1944. The increased number of stillbirths which paralleled the increase in the incidence of abortions and complications of pregnancy, lends added weight to the impression that the stresses of the time told heavily on the reproductive morbidity. It is interesting to compare observations made by Italian medical men in a portion of Italy (Verona) which suffered far less restriction than Naples, but which are reported as showing similar direction to the changes in effects upon mothers and infants to those we present (7). Whether any significance can be attached to the increased number of males born in 1944 and 1945 in totals of this magnitude may be questioned.

Using the statistics for average weights on Italian non-pregnant women collected before the war as a reference standard, it was found that 25% of the pregnant women in our group were below and only 1% above that standard. Since a starchy diet predominated it may be possible that even these weights were influenced by the presence of some tissue edema. Clinical observations support this contention.

The anthropometric data obtained from measurements made within the first three days after delivery are given in Table 3. The standards used are from data on Italian children published by Krogman (8) and these figures were selected for our purpose by Dr. Krogman as being the most accurate for the population group being studied. (It was a matter of mutual regret that Dr. Krogman was not able to be a member of the team working in Italy as had been originally planned). It is clear from these tables that the length and weight of infants of both sexes were decreased significantly in 1944, as compared with 1939. Also there is a consistent tendency in 1945 to return toward the 1939 levels of both length and weight. Evidence of this type of influence of maternal nutritional levels was to have been expected. (4) (6).

TABLE 4

Case Distribution of Blood Plasma Vitamin A and Carotene Levels (in 21 women)

Carotene Micrograms per 100 ml.	Vitamin A, Units per 100 ml. 30-39	40-49	50-59	60-69	70-79	80-89	90-99	100-109	110-120	120+
250-300		1								
200-249	1			3	1	1	1			
150-199			1	3		1		1		1
100-149		1			2	2			1	

In line with observations made by numerous other investigators, we failed to observe any correlation between the blood levels of carotene and of vitamin A (Table 4). The absence of a large proportion of women with strikingly low vitamin A levels is important since the complaint of an extremely low fat diet was universal, dairy fats were rarely available, and fishing had been seriously reduced as a result of the military operations. The use of green colored vegetables, including peppers, is probably responsible for the maintenance of an adequate supply of carotene.

TABLE 3

Measurements of Italian Babies at Birth

	LENGTH										WEIGHT									
	Males (Krogman standard 50.3 cm.)					Females (Krogman standard 48.8 cm.)					Males (Krogman standard 3.23 Kg.)					Females (Krogman standard 3.09 Kg.)				
	46 or under	46-47.9	48-49.9	50+	Totals	45 or under	45-46.9	47-49.9	50+	Totals	3.2 or under	3.2-3.3	3.3 or over	Totals		3.1 or under	3.1-3.2	3.2 or over	Totals	
1939 No.	23	16	62	85	186	16	19	91	53	179	116	40	70	226		117	38	63	218	
%	12.4	8.6	33.3	45.7		8.9	10.6	50.9	29.6		51.3	17.7	31.0			53.7	17.4	28.9		
1944 No.	19	20	22	27	88	12	19	21	16	68	68	10	22	100		50	6	18	74	
%	21.6	22.7	25.0	30.7		17.7	27.9	30.9	23.5		68	10	22			67.6	8.1	24.3		
1945 No.	32	39	74	73	218	30	29	89	35	183	159	35	60	254		143	38	36	217	
%	14.7	17.9	33.9	33.5		16.4	15.9	48.6	19.1		62.6	13.8	23.6			65.9	17.5	16.6		

Difficulty was experienced in correlating skin lesions with possible vitamin A deficiencies, since lack of soap and poor hygiene of the skin were common.

TABLE 5
Blood Plasma Ascorbic Acid Levels in 123 Pregnant Women

Number of Patients	Mg. Per 100 Ml.
3	1.2-1.3
5	1.1-1.19
2	1.0-1.09
4	0.9-0.99
2	0.8-0.89
13	0.7-0.79
8	0.6-0.69
9	0.5-0.59
18	0.4-0.49
21	0.3-0.39
7	0.2-0.29
13	0.1-0.19
5	0.01-0.09
13	None
123	Total

The blood plasma ascorbic acid levels (Table 5) differ widely, and almost one-fourth of the group showed levels of 0.7 mg. or more. Nearly half the women had levels less than 0.4 mg. This wide variation apparently reflects the great individual differences in the use of fresh fruit and vegetable foods. These were usually available in the markets in Naples, although the seasonal supplies of oranges and tomatoes made continuous dependence upon these optimal sources of ascorbic acid impossible for most women.

Attempts were made to establish correlations between the gingivitis observed in 88 per cent of these women, and their ascorbic acid levels. In some women ascorbic acid supplements were given, whereas in others the supplements were either pyridoxine, niacinamide, riboflavin, or vitamin A. We were convinced by subsequent examinations, which were confirmed by Kodachrome photographs in several cases, of definite improvement in the color of the gingivae after the use of at least three different vitamins: ascorbic acid, pyridoxine, and vitamin A. However, conditions did not allow us to make long-term studies on enough of these women sufficient to establish any extensive improvement in the gingivitis.

While examining these women for the commonly recognized evidences of nutritional inadequacy, we seldom saw a woman without several physical stigmata indicative of such deficiencies. It does not seem warranted to present a tabulation showing findings in the sclerae and conjuctivae indicative of vitamin A deficiencies in 80 per cent, facial skin or lip signs suggesting riboflavin deficiency in 51 per cent, or abnormalities of the tongue in 92 per cent since our patients usually had several of these signs. We were unable to establish definite correlations between given findings and specific dietary deficiencies. Loss of turgor and elasticity of the skin were repeatedly observed. Cyanosis of the legs, marmoration and chilblains were common. We were impressed by the reduction of color changes and of peripheral circulatory embarrassment in several women after the administration of vitamin supplements. Riboflavin seemed especially helpful. These findings are not dissimilar to those reported by others from Austria (9).

Pallor of the mucosae which was often very noticeable had no apparent relation to hemoglobin levels. Tenderness of the calf muscles on compression was observed in 49 per cent of the pregnant women, as well as in many other subjects studied by the team.

TABLE 6
Case Distribution of Blood Plasma Protein and Hemoglobin Levels

Hemoglobin (Van Slyke)	Number of Patients	Plasma Protein, Grams per 100 ml.									
		4.8	5.6	5.8	6.2	6.5	6.8	7.2	7.5	7.8	8.6
15-17	8			1	1	1	2		2	1	1
14-14.9	20			2		2	6	7	3		
13-13.9	26		1	2	2	4	6	8	3		
12-12.9	38	1	1	1	7	7	11	7	2	1	
11-11.9	30	1		1	5	12	4	4	3		
10-10.9	7	1	2			1		1	2		
8-8.9	1					1					
6-6.9	1	1									
Totals	131	4	4	7	15	27	29	27	15	2	1

Plasma protein and hemoglobin concentrations, as estimated by the copper sulfate specific gravity method, (Table 6) showed little correlation. Those few individuals with the lower plasma protein levels tended to be in the anemic group (4). The reverse is not true, since there were as many instances of low hemoglobin with normal plasma protein values as there were with significantly low protein.

TABLE 7
Hemoglobin Blood Levels in Pregnant Women

Number of Patients	Grams Per Cent
1	16 - 17
3	15 - 15.9
14	14 - 14.9
22	13 - 13.9
27	12 - 12.9
30	11 - 11.9
24	10 - 10.9
12	9 - 9.9
4	8 - 8.9
1	4 - 5
138	Total

The data on hemoglobin concentrations, as determined by the acid hematin method with the electric colorimeter are given in table 7. Slightly over half of the group had values below 12 grams per cent. According to the careful studies of Wilkins and Blakely (10), the facts that almost all our data are from morning blood samples and that none of the women were under basal conditions, but had often come a considerable distance to the clinic, necessarily afoot, would indicate that these hemoglobin values are maximal for these subjects. Therefore, any apparent anemia in our subjects is the more significant. If the data in table 6 are compared with those in table 7, it becomes apparent that the hemoglobin values estimated by the Van Slyke specific gravity technique are consistently higher than those obtained by the other method. More especially there is less differentiation of hemoglobin concentrations in the group when the specific gravity method was used. The patients on whom the observations were made were the same, with minor

exceptions, and the same blood samples were used for both methods. Unfortunately, the manner of compiling the data does not make it possible to compare the colorimetric hemoglobin data and the plasma protein levels.

SPECIFIC DISEASES

The study (by Dr. Ashton Cuckler) on stool samples which were obtained from a consecutive series of adults who did not have diarrhea at that time, showed that 100 per cent had some parasitic infestation. In the final total of his series of 363 individuals (which also included children) 83 per cent had parasites. Single stool examinations were done using simplified techniques which are known to detect parasites in approximately 75 per cent of those demonstrably infested. It is, therefore, substantially correct to assume that all the Italian population under study carried some parasites in the digestive tract. In this series the average number of types of parasitism per person was 2.43. We cannot offer any data which would contribute to the solution of the problem of the extent to which such parasitism causes malnutrition, and also to what extent malnutrition increases the susceptibility to infestation.

According to the Clinica Ostetrica records there was an increase in positive Wassermann test results from 5.7 per cent in 1939 to 42.4 per cent in 1945, in hospitalized patients.

The tests were done by Italian personnel using the same methods in both years. At the time our studies were made the City of Naples still maintained at least one functioning treatment clinic (for syphilis) where patients received therapy at a very low cost but by 1945 the necessary drugs were scarce and of the older variety. Since the war had disrupted even diagnostic facilities such as the Wassermann Tests, it is certain that most of these cases were diagnosed incidental to an examination made in one of the University clinics or hospitals receiving some outside aid.

COMMENTS

In accord with several reports from other areas studied in the period of the Second World War and immediately thereafter, reviewed by Keys (11), we saw extensive malnutrition in Italy among women and infants, but few evidences of classical under-nutrition syndromes. The deficit in calories and in protein foods was most easily discerned, and when findings suggested vitamin deficiency the pictures seen were commonly those of multiple lacks. The apparent correlation between this condition and increased maternal morbidity, infant mortality, and smaller size of infants provides further evidence of the vulnerable status of expectant mothers in any consideration of human nutrition. We cannot escape the impression that a far worse nutritional picture would have been seen but for the world wide attention to such items as the extraction ratio of cereal grains for flour, use of legumes and other vegetable substitutes for animal protein, and the importance of fresh foods as sources of vitamins. The extent to which thorough organization of the efforts in planned nutrition can benefit the national health have been seen in fortunate contrast to our experience in Italy by those who have reported the results of planning through the long period of stringency in the United Kingdom (12). The smaller scale experimental data from Toronto (13) are similarly pertinent.

ACKNOWLEDGEMENTS

It would be difficult to list all those members of the Italian staff whose co-operation was so important in this project. Drs. Renato Ferolo, Vincenzo Baffi and Mario Saggese worked with Miss Dorothy Hagedorn and Miss Marjorie Knowlton of the American staff in hematology and blood chemistry. Dr. Elvira Barbagallo performed the serological tests. Dr. Pasquale DeCaprio worked directly with Miss Ruth Flumerfelt, the American dietitian, and Miss Gordano, as interpreter, instructing the Italians in dietary supplementation as it had been prescribed. Miss Lucia Mercogliano was the indispensable interpreter and clinic assistant throughout the project. The co-operation of Drs. I. Schaur and M. Mesler, in dental examination of these women, and of Drs. Coiro and Siciliano, their Italian assistants, as well as of Mrs. Giula Codagnone, as interpreter, were indispensable.

Without the generous contributions from a number of American firms the feeding program could not have been carried out. The staple foods supplied by UNRRA were supplemented on occasion by bread and pasta including 10 per cent of low fat or full fat soya flour, supplied by the Staley Co., Decatur, Ill., or 10 per cent wheat germ, corn germ, or sunflower seed as flours supplied by Viobin, Inc., Monticello, Ill. These adjuvants were blended with the 70 per cent, unenriched wheat flour supplied by UNRRA by the courtesy of the Barbato Brothers Mill in Naples. A large supply of powdered whole milk, KLIM, in 5 pound tins, was provided by the Borden Co.; Mead, Johnson and Co., provided percomorph oil; Smith, Kline and French supplied Feosol tablets. Large quantities of synthetic vitamins were provided by the Abbott, Hoffmann-La Roche, Merck, and Squibb laboratories.

SUMMARY

The clinical and laboratory data presented are based upon the study, in Naples, of 680 women during the third trimester of pregnancies occurring in the latter half of 1945. All the deliveries were in the hospital (Clinica Ostetrica).

Accompanying the expected increase in the number of pregnancies, there were definite increases in the incidence of stillbirths, abortions, toxemias and other complications.

The length and weight of the Neapolitan newborn in 1944 were significantly less than in 1939. In 1945 these values began to return toward the earlier values.

Evidences of nutritional handicaps in these pregnant women included: (1) obvious weight losses; (2) frequent low hemoglobin levels; (3) physical signs of chronic avitaminoses such as those characteristic of vitamin A, thiamine, riboflavin, niacin, and ascorbic acid deficiencies and (4) numerous instances of very low plasma ascorbic acid level.

An apparent definite increase in the occurrence of syphilis was found and essentially universal intestinal parasitism was detected.

These observations support the emphasis placed by the United Nations Relief and Rehabilitation Administration on their conviction that pregnant women are one of the nutritionally most vulnerable groups and who should, therefore, receive priority in the distribution of nutritional supplements. The findings indicate, however, as other and more extensive studies have shown that supplementation must begin far earlier than the third trimester if it is to be effective.

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Nutrition Notes And Abstracts On Nutrition

EATING WHAT THE FARMER PRODUCES

If a larger proportion of what we eat came directly from the farm, we would be better off and the farmer infinitely so. Agriculture is one of the most unstable elements in our economic system, as evidenced by the fact that the government is obliged to support farm prices in order to avoid a general collapse of the national organism. During the stimulus of war-time there was no particular problem of disposing of farm produce, but it requires only a slight "recession" in our economy to produce unemployment, comparative poverty and belt-tightening all down the line. This is at once, - - and rapidly - - followed by sagging prices on farm products, and lowering of the land values everywhere. The ancient friction between industry and the farming community is unavoidable in a vital nation which, while pre-eminently industrial, is agriculturally more than self-sufficient. Our trouble is that we cannot comfortably dispose of all that we actually produce. The nutrition levels of the population must be raised. People must place a greater value on food, particularly the natural foods, if the farmer is to compete successfully with luxury goods. Since the idea of crop restriction is widely unpopular even with the majority of farmers who are paid by the government to "rest" their acreage, it is worth while attempting not only an increased consumption but a wider distribution of farm products. The key to this achievement lies entirely in popular education in nutrition, and all that we know about the medical aspects of eating proclaims the innate common sense of such a plan. There are too many people among us who eat too much now, but there are those who eat too little, and also others who scarcely ever eat what is good for them. Natural, fresh farm produce is the answer, not only economically but medically, too. At each season of the year there are thousands of communities almost in every state who simply cannot obtain a wide variety of farm products. Privately-owned truck companies could employ vacant trucks winter and summer in a two-way, North-South, profitable haulage. A crop failure in Canada could be wiped out in 5 minutes by a reasonable and temporary relaxation of customs, negotiated at Washington, D. C. This would unload some of our surplus and could be easily matched by American dollars spent on Canadian pulp and minerals.

PROTEIN FOR BREAKFAST

There is a type of obesity, usually encountered in women at the menopause, in which polyphagia depends upon a recurring low blood sugar, although no pancreatic or cerebral lesion is present. Whether hypogonadism has any bearing on these difficult-to-handle cases is questionable. On the other hand, nervousness may well be a factor, particularly if, as so often happens, increased gastric motility results. The latter produces a "dumping" mechanism which results in rapid increase in blood sugar levels, pancreatic over-response and mild, transient hyperinsulinism with consequent hypoglycemia, hunger and faintness. Since eating frequently is the usual solution, self-discovered by the patient herself, adiposity soon develops. Sedatives are of some service and it is customary also to administer estrogenic hormone. However, a dietary inquiry will very frequently reveal that the patient's customary breakfast is merely coffee, or coffee plus carbohydrate in some form. As a matter of fact, this deficient kind of breakfast has often been adopted for the purpose of reducing the weight, but, for reasons stated, it completely defeats its purpose and occasions the patient distress of a needless variety. It is an empirical fact that a breakfast containing considerable protein (say 25 grams) will, in the majority of these cases, do away with the condition. The more gradual release of carbohydrate

for absorption is the theoretical, if not the actual explanation of the improvement.

On general principles, quite apart from the particular type of case referred to, it is the growing consensus of opinion among nutritionists and clinicians that the day of the skimpy, one-sided breakfast is, or ought to be, past. The protein of milk, bacon and eggs is of good biological quality and a breakfast containing them is better for any individual whether he is adipose or normal, because it is between breakfast and lunch that about half of the entire day's work energy is expended.

NUTRITION WITHIN CHINA

H. C. Hou* in a recent issue of Nutrition Reviews gives us a rather clear and concise notion of what the people of China eat and the deficiencies from which they suffer, from the standpoint of an academic nutritionist who, during the Japanese war, was actively engaged in field work. The country is so vast and studies have been so limited that it may be said that there exists no accurate knowledge of the incidence of deficiency diseases in this great nation, but it seems to be a safe inference that they are indeed wide-spread. The dietary habits vary from place to place. In the central and southern portions of China rice is a staple of diet and sometimes the only food, and here beri-beri is common, while in the north where wheat and other cereals displace rice the incidence of this disease is low. Vitamin A deficiency is common everywhere, perhaps owing to the scarcity of fat with consequent poor absorption of carotene. Riboflavin deficiency seems to be ubiquitous while vitamin D lack is more commonly met in the north, because in the milder climate of the south there is greater all-year exposure to sunshine. Pellagra and scurvy are rare in China except during periods of stress. The diet everywhere is low in vitamins, fat, animal protein and calcium, and the small stature of the people may indeed be related to limited protein and calcium intake. Iron deficiency anemia is strangely uncommon. The goiter areas are those far removed from the coast.

Beri-beri is historically recorded from the 4th century A. D. onward, and in the 7th century, a manuscript gave methods of preparing rice polishings for the treatment of the disease (which for some reason reminds us that Benvenuto Cellini was cured of syphilis by being intentionally poisoned by mercury, although his physician apparently did not report the phenomenon). Beriberi is most common in the south where a highly polished rice is preferred and where the eating of raw fish is common, with its intake of thiaminase. During the early part of the Japanese war, riboflavin and niacin deficiency were very common, but pellagra almost disappeared in Shanghai after 1943. Keratosis of the skin and xerophthalmia are very common as is also a mild form of night blindness, the latter quickly responding to vitamin A medication.

*Nutritional Diseases in China, Nutr. Rev., July 1949, Vol. 7, No. 7, 193-195.

Rice forms a fairly satisfactory basis of diet if eaten with greens and pork. Pig raising should be encouraged as it lends itself to the economy, but a large scale dairy industry is impossible because pasture land is not available within reach of transportation outlets. Possibilities exist for a greater utilization of soy bean products and the tremendous egg production of China suggests the advisability of trading eggs for skimmed milk powder. Improvement in China's program depends upon increased transportation facilities and augmentation of the fishing industry. Already popular educational programs in nutrition are at least in the draft stage. Hou feels that a great deal could be accomplished under permanent conditions of peace.

MENEGHELLO, J., ESPINOZA, J., AND CORONEL, L.: *Value of biopsy of the liver in nutritional dystrophy (evaluation of treatment with choline and dried stomach).* (Am. J. Dis. Child., August 1949, Vol. 78, No. 2, 141-152).

By "nutritional dystrophy" the authors refer to a condition of malnutrition in infants characterized by edema and pellagra-like skin lesions, caused by insufficient protein and vitamin intake, and usually referred to in the United States as nutritional edema. Of their 31 cases (average age 14.6 months), 29 showed fatty liver, thus bringing the cases into line with the "infantile pellagra" of Gillman and Gillman in South Africa. 89 biopsies were made without accident. Patients with grade I (least severe) fatty degeneration of the liver had slower and less complete regression than patients with more severe lesions (grade II). Grade III represented a residual lesion and was present only in one case. Clinical improvement, following feeding therapy, generally precedes regression of the hepatic lesions. No difference in the clinical course of hepatic improvement was noted among patients treated with dried stomach, choline or all-inclusive nutrition. (The Gillmans concluded that dried stomach was the treatment of choice). This work proved that no parallelism exists between the functional involvement and the intensity of the hepatic damage.

STONE, S.: *The therapeutic and prophylactic administration of wheat germ oil (vit. E) in infancy and childhood.* (Arch. Pediat., May 1949, Vol. 66, No. 5, 189-200).

Vitamin E in the form of wheat germ oil has proved beneficial in a large group of children with a variety of neuromuscular disorders and other disturbances of the nervous system — muscular dystrophy, myotonia congenita and retarded motor maturation, as well as in anterior poliomyelitis with moderate muscular atrophy. In normal children it produces improvement in health, muscle tone, alertness and intelligence and it appears that vitamin E is required for the maintenance of integrity of the mesenchymal tissues and is important in fat and protein metabolism, exerting also a synergistic effect with vitamin A, certain B factors and C and K. Its administration

is safe and should be included as a regular supplement in view of the inadequate contents of the average diet in vitamin E.

SEYLE, H., STONE, H., TIMIRAS, P. S. AND SCHAFFENBURG, C.: *Influence of sodium chloride upon the actions of desoxycorticosterone acetate.* (Am. Heart J., June 1949, Vol. 37, No. 7, 1009-1016).

Rats maintained on a sodium-free and chloride-free synthetic diet tolerated otherwise fatal doses of desoxycorticosterone acetate (D.C.A.). Sodium chloride deficiency was most effective in preventing the renal and cardiac enlargement, nephrosclerosis, myocarditis, hypertension, and peri-arteritis nodosa normally caused by excessive amounts of D.C.A.; it failed, however, to prevent atrophy of the adrenal cortex and pituitary, which results from overdosage with this corticoid. It is concluded that sodium is essential for the renal, and through the intermediary of the kidney, for the cardiovascular actions of D.C.A.

Editorial

REBELLION AGAINST THE LABORATORY

Medical editors throughout the world are receiving, with increasing frequency, letters from physicians which indicate a growing dislike of the emphasis which modern medicine has placed on the work of the chemical, x-ray and cardiographic laboratories. They express a feeling that the "machine-made" diagnosis is somehow inferior to one arrived at by the unassisted wit of the "pure" clinician. They infer a vague fear that some day the problems of diagnosis may be handed over entirely to the laboratory to the detriment of the clinical physician. In some of these letters is to be discerned a nostalgic yearning for the return of that phenomenal product of the ages, - - - the highly educated physician of vast experience who, through observation, comparison and deductive reasoning was able, without scientific assistance, to arrive at a reasonably accurate diagnosis in perhaps the majority of the cases he encountered.

There are two fallacies in this attitude. The first error is the assumption that any diagnosis *can* be machine made. No matter how valuable the laboratory data in a given case may be, it has to be fitted into the general picture of the individual under investigation, and this can only be done by a physician acutely aware of every phase of the case. In other words, laboratories, though their work should expand a hundred fold, will be proportionately dependent upon the clinician who can evaluate their reports.

The second error is in supposing that the clinical stalwart previously mentioned ever will return. He made miraculous use of his hands, thermometer and stethoscope only because he was forced to do so. While his work was impressive and dramatic, and occasionally his diagnosis astonishingly clever, there were cases which he could not diagnose easily or quickly and in which he had to depend on the course of the disease or the post-mortem findings. There is, by contrast, nothing impressive or dramatic about a four-plus Wassermann, a filling defect on the greater curvature of the stomach or a cardiogram showing the occlusive phenomena, but such findings are potentially very valuable to the physician and particularly the patient.

In the modern medical set-up there are only two dangerous individuals, - - - the laboratory man who knows too litttle about medicine, and the physician who knows too little about the laboratory. It is the *negative* laboratory report which may cost the patient his life in case the physician has worshipped too trustingly at the shrine of the micro-voltometer, the test-tube and the radiant screen. The physician ought to continue proficient in the purely clinical phases of illness, but he has the added responsibility today of acquiring an actual working knowledge of laboratory procedures, their possibilities and their limitations. We cannot do without the laboratory any more than the laboratory can do without us.

Book Review

REGIONAL ILEITIS. By Burrill B. Crohn, M. D., 229 pages, Grune and Stratton, New York, 1949, $5.50.

The man who has had the most to do with orienting the profession to a vague disease which, under his teaching and research, has become a very definite entity, has written a very clear and informative book embracing regional ileitis, chronic and acute, ileo-jejunitis, and ileocolitis. Regional ileitis certainly ought to be designated "Crohn's Disease" but the author does not indicate his consent and generously draws upon the wide-spread experience of other gastro-enterologists which, along with his own, may be said to represent a firm basis for this clinical entity whose etiology still is quite obscure. The roentgenological diagnosis is stressed and the volume is profusely illustrated with x-ray pictures and pathological specimens. The matter of treatment is completely covered. The possession of this volume is the physician's best insurance against slipping up on the diagnosis of this remarkable malady, and everyone ought to study it.

FRANZ J. LUST.

BRIDGES' DIETETICS FOR THE CLINICIAN. By Harry F. Johnson, M.D., F.A.C.P., 898 pages, Fifth Edition, Lea and Febiger, Philadelphia, 1949, $12.00.

Former editions of this valuable treatise have been reviewed in these columns. The present Fifth Edition represents a thorough revision and re-editing. A new chapter has been added on folic acid, and revision has been made under more than twenty subjects, including vitamins, chemical food analysis, diet in arthritis, hypertension, spastic colon, disease of the liver, angina pectoris, myocardial failure, rickets, constipation, coronary thrombosis and other conditions met in general practice. The book is both reliable and exhaustive from the standpoint of practical medical dietetics. Diseases are approached alphabetically for convenience and methods given for figuring diets of any conceivable type. The Complete Food Tables are of value both in practice and research. Everyone connected with medicine ought to procure this masterly work.

DIAGNOSTIC TESTS FOR INFANTS AND CHILDREN. By H. Behrendt, M.D., 529 pages. Interscience Publishers, Inc., New York, 1949, $7.50.

This extremely useful volume is a compilation of function tests of extremely wide application, written from the standpoint of pediatric practice. The digestive tract, including hepatic function is thoroughly covered, as well as carbohydrate, fat and protein metabolism. Vitamin nutrition tests form a valuable section, and the thoroughness of the work is indicated by the inclusion of cardiovascular tests, immunological examinations, renal function tests, endocrine function and even psychological tests. It would appear that the author has produced a book which no pediatrist should be without.

ADVANCES IN SURGERY, VOL. I. 544 pages, Interscience Publishers, Inc., New York, 1949, $11.00.

The distinguished editorial board who have fathered this first volume of Advances in Surgery have gone far afield for their contributors and have selected those surgeons who are known to be prime authorities on the topics which they individually discuss. The book deals with traumatic shock, common duct strictures, nerve regeneration, antibiotics, the immersion foot syndrome, blood vessel anastomosis and bone tumors. Each author has produced an authoritative monograph and emphasized the more recent developments in his subject. For the surgeon, this volume will prove a pleasure.

ADVANCES IN INTERNAL MEDICINE, VOL. 3. 478 pages, Interscience Publishers, New York, 1949, $8.50.

Under the editorship of William Dock and I. Snapper, volume 3 presents a number of extremely valuable contributions including the following subjects, — the use of BAL in treatment of poisoning by arsenic, mercury and other metals; current concepts of hemolytic anemias; host, drug and parasite factors that modify the therapeutic activity of penicillin; streptomycin: development and status of its use in the treatment of tuberculosis; histoplasmosis; treatment of hyperthyroidism with anti-thyroid compounds; diagnosis of disease by enzymic methods; plasma fractionation; the mechanism of acclimatization to heat; modern therapeutic agents used in neurological conditions. The authors are all prominent authorities on their subjects.

THE VALUE OF HORMONES IN GENERAL PRACTICE. By W. N. Kemp, M.D., 115 pages, ($3.00), Burgess Publishing Co., Minneapolis, Minn., 1949.

This is an ably written book by a Canadian physician who has devoted considerable time to endocrine research and knows "his way around". It has the advantage of brevity and covers the whole field of hormones in 115 large-sized pages. It is pleasant reading and one service which Kemp gives the student is to clarify the multitude of trade names which have been applied to the hormones by various pharmaceutical organizations. It is heartily to be wished that all writers on endocrinology would condescend to do likewise because the average practitioner is more or less confused by trade-names today and scarcely knows what preparation to use for a given purpose. A single example of Kemp's insight may be seen in his statement (which derived from his own investigations) that unexplainable stillbirths are 6.3 times more common among mothers in Vancouver, B. C., who have received no extra dietary iodine in the latter months of pregnancy. The text is printed in type-writer face and bound by wire coil to facilitate frequent low cost revisions. The book is written for the practitioner, and

ought to be in everybody's hands who desire a succinct and reliable guide in this important phase of practice.

PHENOL AND ITS DERIVATIVES: THE RELATION BETWEEN THEIR CHEMICAL CONSTITUTION AND THEIR EFFECT ON THE ORGANISM. By W. F. von Oettingen, (U.S. Public Health Service). 408 pages. U. S. Government Printing Office, Washington, D.C., 1949, price 70 cents.

This volume concerns itself with the chemical constitution of phenol and other *monophenols* such as cresol, thymol and naphthol, as well as diphenols, among which are resorcinol and hydroquinone, the *triphenols* such as pyrogallol, the *helogenated phenols,* the *aminophenols,* the *nitrophenols,* the *phenolic aldehydes, phenolic acids,* and the *phenolic ethers,* and also with effects on living matter where these have been observed. A very extensive bibliography is included. The book will be of value to all chemists and pharmacologists.

CONFRONTATIONS: RADIO-ANATOMO-CLINIQUE, VOL. III. By M. Chiray, R. A. Gutmann and J. Seneque, 80 pages, Masson et Cie, Paris, France, 1949.

The glossy pages of this beautiful album of x-ray and pathologic half-tone engravings measure 10 x 13 inches. The essentials of a case are given, including the complaints, symptoms and physical findings, then follow reproductions of the roentgenograms from which one may attempt to make a diagnosis. Following this comes a general discussion of the case and, in many instances, autopsy reports and beautiful specimen and slide illustrations of the pathological material. A goodly proportion of the cases are gastro-enterological, but a subsidiary position is given to bone pathology, respiratory disease and renal tuberculosis. This is a good method of studying diagnosis, and the book is highly recommended, though written in French.

SING, K. G.: *Nutrition survey in Ghandi Nagar Camp, Jullundur.* (J. Indian Med. Assoc., Jan. 1949, Vol. 18, No. 4, 96-99).

The survey was made December 1947 when Gandhi Nagar Camp had been in existence for 4 months and was daily admitting fresh arrivals. Of 6,000 refugees examined, 8.3 percent, chief men, gave evidence of nutritional deficiency. The scale of rations in the camp could not be increased above 1370 calories per diem at the time of the report. Pure vitamin C and pure vitamin D deficiencies were negligible. Vitamin B Complex was the chief deficiency although symptoms suggesting lack of vit. B_2 alone were very common. It is remarkable that 440 cases showed myxedema. Many associated diseases, particularly dysentery were present. Remarkably good results were obtained by giving a multivitamin pill (Brewer, U. S. A.) 6 per diem. The explanation of the myxedema, which was distinguished from nutritional edema, was impossible to give at the time the report was made. The author recommended that the camp use regular rations of germinated grains, ground nuts (peanuts) for their nicotinic acid content, eggs and minced liver.

MOSBY'S COMPREHENSIVE REVIEW OF NURSING. 704 pages, The C. V. Mosby Co., St. Louis, Mo., 1949, $5.75.

This huge volume (the pages measure 8½ x 11 inches) is a "study outline" for those nurses, both student and graduate, who desire a clear summary of the subjects taught in the basic courses in nursing. Material has been so selected and presented as to enable the student to integrate basic science courses with the clinical nursing subjects. The book should be priceless as an examination primer for graduates preparing for special examinations. It would also serve for refresher, supplementary or postgraduate courses in nursing. The volume is ably edited. The section on nutrition and diet therapy is extremely complete. None of it is written in paragraph prose but in suggestive notes and headings which can be grasped at a glance.

General Abstracts

PINCUS, P.: *Production of dental caries (a new hypothesis).* (Brit. Med. J., Aug. 13, 1949, 358-362).

After a consideration of the structure of teeth and a review of the current theories of dental caries, the author advances the following facts and hypotheses: between the cusps of molar teeth lie grooves which, especially if narrow, are a common site of caries. These grooves in newly erupted teeth contain two structures which differ in biochemical nature. One is a mucoprotein. Enamel at eruption is covered with a layer of protein, and is permeated with protein throughout life. Enamel protein is a mucoprotein, which comprises a class of proteins containing mucoitin sulphuric acid. Dentine contains chondroitin sulphuric acid. Gram-negative bacilli found in caries can release an enzyme — sulphatase. Sulphatase can release sulphuric acid from such combined forms as mucoitin sulphuric acid and chondroitin sulphuric acid, thus attacking the calcium salts of both enamel and dentine and causing caries. There is some experimental support for the theory.

LAWSON, J. F.: *Tuberculous esophago-cutaneous fistulae treated with streptomycin and gastrostomy.* (Am. Rev. Tuberculosis, June 1949, Vol. 59, No. 6, 687-691).

A case of tuberculous esophago-cutaneous fistulae treated with streptomycin (86 grams over a period of 86 days) was apparently cured, the two fistulae having remained closed for more than 3 months. A gastrostomy was done and for 72 days during the period of chemotherapy the patient was exclusively tube-fed.

DENICOLA, R. R.: *Intragastric oxycel.* (Northwest Med., August 1949, Vol. 48, No. 8, 541-542).

At re-operation to correct intragastric bleeding which followed a gastric resection, it was found that the hemorrhage was coming from an inaccessible part of the fundus, due possibly to ulceration or the irritation of an indwelling Levine tube. The author pulled the Levine tube through the wound and attached to it 5 separate pieces of oxycel by means of ligatures of medium silk. This was then pulled up into the stomach remnant and successfully controlled hemorrhage and permitted a normal recovery. The oxycel gradually deteriorated under the influence of the stomach fluids and was passed via the feces, so that by the fourth post-operative day the Levine tube was removed. This work suggests that if a patient could be made to swallow a tube upon which oxycel was tied, it might possibly constitute a good method in emergency bleeding from peptic ulcer.

CAMPBELL, K.N. AND DARMSTAETTER, A.A.: *Progressive malnutrition with reversal of peristalsis following total gastrectomy and esophagojejunostomy utilizing the Reinhoff modification of the Roux-Y.* (Alex. Blain Hosp. Bull., Aug. 1949, Vol. 8, No. 3, 84-88).

The authors report a case in which, owing to an exceedingly short jejunal mesentery, it was necessary to employ the Reinhoff modification of the Roux-Y to bridge the defect produced by a total gastric resection for carcinoma. After the operation, for three months, the patient regurgitated bile and fecal material and suffered from progressive malnutrition, and eventually died, presumably of a cardiac accident. Special X-ray studies with intubation of the distal limb of the anastomosis showed persistent reversal of peristalsis. Possibly a cholecystojejunostomy to sidetrack bile from the proximal loop would have aided this patient considerably.

MOORE, SHERWOOD: *Mass roentgenological survey of the gastrointestinal tract to detect cancer of the stomach.* (A. J. Roentg. Rad. Th. 61, 4, 470. April 1949).

Moore concludes that with the present state of the art of gastrointestinal examination it must still remain an art and is therefore not suitable for mechanization such as would be the case with mass survey techniques. Although there might be some possibility of detecting cancer of the stomach with this method, it probably would detect only the late cases. The accepted method of examination by the radiologists of this country is highly efficient, and gastric cancer of the one type which seems to be suitable for detection by mass survey methods comprises but a small part of the incidence of gastrointestinal cancer. From the data which have been accumulated, it is obvious that overemphasis has been placed on the incidence of cancer of the stomach.

Franz J. Lust

QUIN, B.: *Vomiting in infancy.* (New Zealand Med. J., April 1949, Vol. 48, No. 264, 151-158).

The chief causes of vomiting in infancy are, thrush, overdistention due to air swallowing, too frequent feeding, too large a volume of food, unsuitable composition of food, tight abdominal binders, parenteral infections, nervous vomiting and rumination, gastroenterospasm, gastrointestinal obstruction, allergy, intracranial states and toxic states. Skin tests are not worth while in suspected allergy of the G.I. tract, and resort must be made to elimination diets. Fortunately, infants are not very prone to travel sickness.

BOLKER, V.: *Early diagnosis of carcinoma of the stomach.* (Annals Int. Med., May, 1949 903-913).

In a very thoughtful paper, the author comes to the unpleasant, but obviously justified, conclusion that none of the present diagnostic methods are practical in increasing the detection rate of gastric cancer at a stage in which a reasonable chance of cure exists. Although X-ray diagnosis is accurate in 91 per cent of cases, most of these cases already present a hopeless prognosis. The early symptomatology of the disease is vague and, in intensity, far below the significance of the threat to life. All ulcer cases, and those persons with a family history of cancer of the stomach and particularly all persons with pernicious anemia should submit to careful periodic gastric roentgen examination.

CULLINAN, E. R.: *Classifications of chronic diarrhea.* (Proc. Roy. Soc. Med., April 1949, Vol. 62, No. 4, 235-239).

The author analyzes 99 cases of diarrhea who have been under his own personal care. 41 of them were instances of chronic idiopathic colitis and in 35 no organic lesion was found. These two groups accounted for more than three-quarters of the total. He feels that both groups demonstrate psychosomatic causes in that the cases in either group can only be understood in relationship to the emotional pattern of the individuals. Excitement, worry, anxiety, fear and fatigue from overwork were often exacerbating causes. Many patients seem to have nothing more than an unduly sensitive colon with exaggeration of the normal physiological response. Allergy was never proved in any of the cases. There was no evidence that achlorhydria, when present, bore any causative relationship to the diarrhea.

KALIL, T. AND ROBBINS, L. L.: *Early roentgenologic changes in idiopathic ulcerative colitis.* (Radiol., July 1949, Vol. 53, No. 1, 1-10).

In an attempt to determine the earliest X-ray signs of idiopathic ulcerative colitis, the authors reviewed X-ray pictures taken in a group of 160 patients in whom the diagnosis was well established. Two signs were found which, when combined, appear to be diagnostic of the early stages of the disease: (1) Thickening of the mucosa, suggested by a change in the normal irregular crink-

ling of the mucosal pattern, and (2) Scattered to multiple tiny serrations along the edge of the bowel. In order to demonstrate these signs, a clean bowel is necessary and films must be taken at a speed sufficient to offset intra-abdominal motion. One film must show a full, but not over-distended bowel.

JONES, J. D. T.: *Perforation of the rectum.* (Brit. Med. J., May 28, 1949, 933-935).

Perforation of the rectum is rare but is usually due to injury by enema tips or during sigmoidoscopy. In all cases, cystoscopy may be needed to determine if there is serious bladder injury. The rectal laceration when found should be sutured if possible, adequate drainage provided, and a temporary colostomy performed. If the bladder is involved, the rent should be sutured and suprapubic or transurethral drainage instituted.

BELLINI, M. A.: *Volvulus of the sigmoid, a new radiological sign.* (Radiology, Aug. 1949, Vol. 53, No. 2, 268-270).

The author describes the radiological picture characteristic of volvulus of the sigmoid and points out a new sign of great value which serves to distinguish this type of colonic obstruction from that due to any other cause. The distinctive feature consists in the uniform diameter of both sides of the arch produced by the distended sigmoid coil.

GROSS, R. J.: *Cauda equina syndrome due to silent rectal carcinoma.* (Radiology, August 1949, Vol. 53, No. 2, 271-273)

The case of a 43-year-old man is presented who suffered pain in the right gluteal region and had a hard, tender mass in the right gluteal region. He gradually lost motor power in the right leg as well as having difficulty in urination and defecation, and showed atrophy of the muscles of the right posterior thigh, absence of the right ankle jerk, and impairment of sensation on the right side over the areas of distribution of the 5th lumbar nerve and all the sacral nerves. The "cauda equina syndrome" in this case was due to a peri-rectal abscess which was evacuted. Later a rectal carcinoma of the posterior wall was discovered. The author emphasizes the importance of lateral X-ray films of the rectum showing the anterior displacement of the rectum so characteristic of the condition. Rectal digital examination had proven unsatisfactory because of the great tenderness present. The patient unfortunately died of peritonitis following a colostomy done prior to palliative X-ray therapy.

SHIELDS, J. J.: *Spread of diarrhea of unknown origin in a ward for infants.* (Am. J. Dis. Child., August 1949, Vol. 78, No. 2, 217-225).

The author describes the epidemic spread of a disease resembling so-called epidemic diarrhea of the newborn as it occurred in the wards of a children's hospital on two different occasions, due, probably, to breaks in isolation techniques. Of the 30 infants acquiring diarrhea during a period of 18 months, 10 died in spite of the usual forms of therapy. The etiology of the diarrhea was obscure. Isolation is the sole means of restricting the disease and should at once be practiced on any infant showing diarrhea.

FAXON, HENRY F. AND SCHOCH, WILLIAM G.: *Gastrojejunocolic fistula.* (New England J. of Med. 240, 3, 81. Jan 20, 1949).

The findings in nine cases of gastrojejunocolic fistula are presented. The symptomatology is usually attributable to the secondary effects of diarrhea induced by the reflux of irritating large-bowel contents into the upper jejunum and stomach. Passage of gastric material into the colon through the fistula in the reverse direction is delayed, as a rule, by a valve-like action of the jejunal mucosa.

The treatment of gastrojejunocolic fistulas is surgical and consists of removing the fistula, restoring bowel continuity and correcting the ulcer diathesis.

Preparation of the patient for excision of the fistula should include the institution of an ascending colostomy as recommended by Pfeiffer as a preliminary procedure in all patients whose general condition is unsatisfactory.

The tendency in these patients to reactivate an ulcer after an excision of the fistula and restoration of intestinal continuity is so strong that unless corrective surgical measures have been carried out at the earlier operation they should be adopted before the patient is finally discharged from the hospital.

A case is cited from the first time in which, after excision of the fistula, transthoracic vagotomy was used as the definitive treatment of the ulcer diathesis. This patient was asymptomatic a year after the vagus resection.

Franz J. Lust

GALLUT, J.: *Specific antigen of cholera vibrio.* (Bull. World Health Org., 1949, 2, 39).

Dr. J. Gallut of the Institut Pasteur, Paris, has made an exhaustive analytical study of the heat-stable antigen of the cholera vibrio (specific O antigen), and his findings have recently been published in the *Bulletin of the World Health Organization.* Confirming research work carried out by Burrows, the author notes that a greater number of O antigenic factors exists in cholera vibrios than has so far been admitted. As many as 13 antigenic factors (A, B, C, . . . M) can be detected. This discovery is very important, as it may enable the accuracy of the serological diagnosis of cholera to be increased, and vaccines to be prepared in such a way as to be better adapted to the various epidemics.

The author analysed 82 strains, which fall into two groups: the first comprising 61 so-called "agglutinable" vibrios, and the second comprising 21 so-called "inagglutinable" vibrios. Following the usual serological diagnosis, the 61 "agglutinable" vibrios were classified as follows: 2 Ogawa, 40 Inaba, 18 Hikojima and 1 atypical. Complete antigenic analysis, however, revealed their multiple O factor content and showed the antigenic differences which may appear between vibrios considered as serologically identical. Antigenic analysis of the second group revealed the presence, in some of the vibrios, of factors found in the first group. Moreover, there are frequency variations in the distribution of these factors, which indicate an essential point: factor A, which is to be found in all "agglutinable" vibrios, has never been found in "inagglutinable" vibrios. For this reason, the

author is in a position to state, in agreement with Burrows, that antigen A is the only specific antigen of the authentic cholera vibrio (and of the El Tor vibrio, which is serologically identical). Experience has also shown that factor A can exist alone, thus making it possible to define a new and fourth type of cholera vibrio. Factors B and C are essential, as they are specific for the Ogawa (B) and Inaba (C) types, but only in a subsidiary way, because of their relationship with factor A. Factors B and C, were, in fact, encountered more frequently in non-cholera vibrios. Factors D, E, . . . M are of less significance. The O antigenic formulae of the "agglutinable" vibrios, and the frequency of O antigenic factors in both groups of vibrios, are summarized in two tables.

These experiments may have important practical consequences:

(a) In diagnosis, anti-O monospecific serum A will have to be used in future in preference to Ogawa and Inaba sera, which are prepared from strains of which the antigenic formula is only partially known. Agglutination due to non-specific factors will thus be avoided.

(b) Complete antigenic analysis of the cholera vibrio may change present views on the preparation of vaccines. In this respect, too, the accepted concept of the Ogawa Inaba and Hikojima types now seem outmoded. If the need arises of using a so-called "monovalent" vaccine to combat an epidemic of a supposedly "single" serological type,[2] it would be advisable to proceed with the greatest possible care and not rely too much on the respective monospecificity of the three classical types.

Antigenic analysis showed that Egyptian cholera vibrios of the 1947 epidemic, nearly all of the Inaba type, contained all the factors except B, G and J, with factors A, C, D, E and L predominating. For this reason, Dr. Gallut is of the opinion that not only does a mixed vaccine composed of one Ogawa and one Inaba strain appear to be inadequate, but a vaccine composed of the Inaba type alone might be partially ineffective if it contained only the two factors A and C, specific for this type, and none of the subsidiary factors. According to the author, the solution so far adopted of preparing vaccine from strains isolated during the epidemic against which control measures are being taken lacks precision. If the overriding necessity of having a completely polyvalent vaccine in stock, comprising the 13 O factors, is admitted, it would seem logical to take into account the antigenic composition of the vibrios responsible either for endemic cases or a specified epidemic. Moreover, it would be advisable to make a selection from those strains containing all the required factors, by quantitative titration of the total O antigenic content of each one, thereby ensuring the production of a vaccine with maximum specific immunizing properties.

(2) Chr. World Hlth. Org., 1948, 2, 117.

MACNAB, I.: *Subacute pancreatitis.* (Brit. Med. J., April 2, 1949, 568-571).

Patients suffering from subacute pancreatitis present as an acute abdominal emergency but settle down on conservative treatment. The condition is very likely to recur. Of the 19 cases presented, 13 were recurrent attacks. The estimation of the serum-amylaze level should be more widely employed to differentiate this condition from other acute abdominal lesions.

MATHESON, W. J.: *Fibrocystic disease of the pancreas.* (Brit. Med. J., July 23, 1949, 206-210).

The author reports seven cases of fibrocystic disease of the pancreas in some detail. He repeats Farber's findings that dilated glandular structures occur elsewhere beside the pancreas, e.g., in the bronchial tree and the wall of the gut, but does not offer any hypothesis to explain this wide spread pathological state. He believes that the bronchial infections which terminate life are dependent upon the abnormality of the mucous glands in the air passages and that, inasmuch as antibiotic and sulfonamide therapy institute no cure for these infections, a rational treatment would consist in liquefying this mucus by some substance such as hyaluronidase. He feels that a firm diagnosis can be made from careful history and clinical examination without duodenal intubation. Pancreatin has great therapeutic value but casein hydrolyzates have still more, though their taste prevents their use in older children.

GARDNER, H. T., ROVELSTAD, R. A., MOORE, D. J., STREITFELD, F. A. AND KNOWLTON, M.: *Hepatitis among American occupation troops in Germany: a follow-up study with particular reference to interim alcohol and physical activity.*. (Ann. Int. Med., May 1949, 1009-1019).

The authors studied 114 American soldiers six months to one year after hospitalization for an attack of infectious hepatitis acquired in Germany. Of these, 46 had been discharged from the hospital with slight residual abnormality and 68 as presumably cured. Only slight differences were noted between the two groups on re-examination after interval, and there were relatively more residuals in those discharged with slight residuals. When re-examined with particular reference to their interim activity and alcohol, it appeared that neither of these factors played a significant role in the appearance of residuals in either group.

MARNER, I.: *Hepatitis and polyarthritis.* (Nordisk Med., Nov. 19, 1948, Vol. 40, No. 47, 2151-2153).

Of 485 patients treated for hepatitis during the past 18 months in two Copenhagen hospitals, 12 per cent had polyarthritic syndromes in the pre-icteric stage, and the joint symptoms usually subsided when jaundice began to appear. There was one case where chronic polyarthritis set in during an attack of acute hepatitis which developed into chronic hepatitis.

ROUSE, M. O. AND LYDAY, V. I.: *Cholecystopathies from anomalies of the gall bladder and its ducts.* (Texas State J. M., Jan. 1949, Vol. 51, No. 1, 10-14).

The author summarizes the various anomalies of the gall bladder and bile ducts which have a bearing upon

clinical work. Among various shapes of gall bladder morphology, he describes the Phrygian cap, diverticulum, pseudodiverticulum, multilobes, double gallbladder, also the hourglass, trabecular and rudimentary gallbladders. Among abnormal locations, he mentions the intrahepatic, floating, retrodisplaced and left-sided gallbladders. Several anomalies of the biliary ducts are described. The writers suggest that all interested radiologists, gastroenterologists, surgeons and anatomists keep accurate records of all anomalies met with in the next few years in order that a comprehensive joint compilation of this knowledge be made. Such information might be forwarded to the authors at 1108 Medical Arts Bldg., Dallas, Texas.

EIKEN, M.: *Gastric ulcer in cincophen poisoning.* (Nordisk Med., Dec. 3, 1948, Vol. 40, No. 49, 2264-2266).

A literature survey of gastric ulcers following cincophen poisoning is recorded, and a case is presented in which the ingestion of 106 grains of cincophen resulted in the formation of a gastric ulcer. The author suggests that caution be exercised whenever cincophen is therapeutically employed.

ABRAMSON, L.: *Ulcer in the aged.* (Nordisk Med., Nov. 26, 1948, Vol. 40, No. 48, 2206-2211).

In a series of 155 cases of peptic ulcer in aged persons, the earliest symptoms began in 40 percent of the cases after 60 years of age. Histamin refractory achylia occurred in only 2 cases of gastric ulcer and not in a single case of duodenal ulcer. Two-thirds of the group were satisfactorily treated by conservative medical methods of management and in this way they did not differ from peptic ulcer in younger individuals. However, thirteen percent of the series proved intractable, because of frequent relapses and severe pain, and these individuals ought to be treated surgically when their general condition permits. In only one case of gastric ulcer could a diagnosis of a mutation to cancer be made and for this reason, the author feels that gastric peptic ulcer should receive conservative medical treatment without incurring much jeopardy to the patient or causing much misgiving to the physician.

SEELEY, S. F., HOGAN, E., HENRY, J. R. AND BERTRAM, H. F.: *Non-operative treatment of perforated duodenal ulcer.* (Bull. U.S. Army Med. Dept., Feb. 1949, Vol. 9, No. 2, 124-130).

Thirty-four cases of perforated duodenal ulcer were treated on the surgical service of the Brooke General Hospital, Fort Sam Houston, Texas, without operation. There were no deaths. Only three complications occurred,—one of right pleural effusion, one of right pleural effusion with subphrenic abscess, which was drained, and one of subphrenic abscess which resolved spontaneously. The authors recommend rigid adherence to the method which they outline. The essential features in the treatment are continuous effective gastric decompression, intravenous fluids and the administration of penicillin and sodium sulfadiazine. The non-operative treatment of ruptured peptic ulcer can be used in the majority of cases with a resulting lowered mortality, a decrease in the time lost from work, a lowered complication rate, and an easier convalescence for the patient. This method is of practical use for cases that occur in places where adequate surgery cannot be performed. This method of treatment should, however, be used only where the patient can be closely observed or where operative treatment is unobtainable.

COHEN, S. AND MA, Y. Y.: *Supplementary oral protein hydrolysate therapy in tuberculosis.* (Am. Rev. Tuberculosis, May 1949, Vol. 59, No. 5, 519-538).

Protein hydrolysates containing varying amounts of amino acids were used to supplement the regular hospital diet in six tuberculous patients who had shown an unfavorable clinical and roentgenological course. Three patients showed significant constitutional response with gain in weight. The pulmonary lesions were improved in two and stationary in one. Hydrolysates may well be used in patients who show evidence of clinical deterioration, or who need building up preliminary to chest surgery. The hydrolysates are unpleasant to swallow and the author wonders if protein concentrates such as casein or wheat germ could not be used to achieve the same effects.

HIPSLEY, E. H.: *Some aspects of nutrition as related to the practice of obstetrics and gynecology.* (Med. J. Australia, June 11, 1949, 775-781).

As a result of a careful study of the problem of nutrition in pregnant women, particularly, the author is not impressed by the idea, put forward by several authors, that eclampsia is most likely to occur in women partaking habitually of a low protein diet. He cites the example of the New Guinea natives, whose diet is not only deficient in protein, but whose protein is of poor biologic value, but who are particularly exempt from eclampsia. He believes rather that the level of magnesium in the diets of normal and toxemic women deserves wide investigation. He also presents several facts to strengthen the conception that a deficiency in magnesium may be etiologically important, one of which is the good effects of injections of magnesium sulfate in eclampsia. He also found a statistically significant difference in the magnesium intake of 20 toxemic women as compared with normals.

KIRKPATRICK, N. R.: *Experience with a new insulin.* (Proc. Staff Meet. Mayo Clin., July 6, 1949, Vol. 24, No. 14).

NPH50 is a neutral crystalline protamine zinc insulin with an action intermediate between that of soluble (regular) insulin and protamine zinc insulin. In using it in 20 cases of severe diabetes, decidedly better control and greater convenience was experienced. Wilder, in discussing the paper stressed the point that NPH50 does not require any excess of protamine for stability, therefore soluble insulin can be added to it as needed without loss of quick action. He believes NPH50 is simpler and much safer and will completely replace protamine zinc insulin.

SCHERING APPOINTS FOX ASSISTANT TO PRESIDENT

The appointment of Mr. Mortimer Fox as Assistant to the President has been announced by Mr. Francis C. Brown, president of Schering Corporation, pharmaceutical manufacturers of Bloomfield and Union, N. J.

Mr. Fox comes to Schering from the Indian Motorcycle Company of Springfield, Mass., where for the past three years he was Treasurer and Controller since his honorable discharge from the U. S. Army. Prior to this, Mr. Fox served with the War Production Board where he was simultaneously for almost a year Regional Statistician in Detroit and Research Advisor to the Automotive Branch in Washington. He enlisted in the U.S. Army in 1942 and was promoted through the ranks to the grade of Captain of the Air Corps. His duties included budget and supply in addition to serving in Washington at the Pentagon Building as statistical officer. Mr. Fox earlier was for five years economist for the investment trust, Tri-Continental Corporation of New York.

A graduate of Yale University, Mr. Fox later graduated from Harvard Business School with his master's in business administration.

CORICIDIN SUCCESSFUL AGAINST COMMON COLD

Coricidin tablets, for aborting and treatment of the common cold, are now available from Schering Corporation, pharmaceutical manufacturers of Bloomfield and Union, N. J. It is the first preparation using the combined antihistaminic - analgesic - antipyretic attack against coryza.

The principle ingredient in Coricidin is Chlor-Trimeton, Schering's new, potent antihistaminic drug. Each Coricidin tablet contains 2 milligrams of Chlor-Trimeton. Included are adequate amounts of acetylsalicylic acid, acetophenetidin and caffeine which contribute their well known analgesic-antipyretic synergistic effects.

According to the *Journal of the American Medical Association* (September 10, 1949, "Current Comments", page 138): "The common cold is an allergic response in susceptible persons to contact with a specific protein, which is the cold virus or its products."

This relatively new concept of the cold was understood and investigated by several clinicians in the last few years resulting in definite clinical proof. Captain J. M. Brewster, in charge of the cold clinic at the U. S. Naval Hospital at Great Lakes, Illinois, reported in the U. S. Naval Medical Bulletin on the outcome of antihistaminic treatment for colds in 572 patients. He found, "A cold was considered to have been aborted or cured when all signs and symptoms disappeared completely within 24 hours of the beginning of treatment and remained absent for at least 48 hours after all treatment was stopped. All symptoms were aborted in 90 percent of the patients in whom treatment with antihistaminic drugs was begun within the first hour after onset of symptoms, and in 87 percent of patients treated within two hours of onset; 74 percent of patients who received treatment within six hours, and 70 percent of patients who received treatment within 12 hours of onset were also cured." Other studies showed similar results.

The combination of pharmacologic effects in Coricidin Tablets provides the ideal therapy for the management of the common cold. Dosage indicated for adults is two tablets at the very first indication of cold symptoms followed by one tablet every three or four hours for three or four days, as necessary.

RESEARCH FELLOWSHIPS — THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1950-June 30, 1951. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1949. Announcement of awards will be made November, 1949.

CIBA AWARD

The annual Ciba Award for outstanding work in clinical endocrinology has been awarded this year to Dr. George Sayers. The selection was made by a committee of the Association for the Study of Internal Secretions and announced at a recent dinner. It is expected that the work of Dr. Sayers will have an important use in the study of the effects of cortisone and ACTH in arthritis and rheumatic fever.

Dr. Sayers developed a new and sensitive method for the assay of the adrenocorticotropic hormone of the anterior pituitary gland. He found that the ascorbic acid and cholesterol content of the adrenal glands varies inversely with the amount of ACTH administered to the test animal. Having established the method, he applied it to the problem of pituitary-adrenal relationships. The interrelation of the pituitary and the adrenal cortex, and the response of this hormonal system to a variety of stimuli are better understood and can be better studied as a result of his investigations.

Dr. Sayers was born in 1914. He received the degree of M. S. in physics from the University of Michigan in 1936 and the Ph.D. degree in physiological chemistry from Yale University in 1943. From 1943 to 1945 he served with the Office of Scientific Research and Development at Yale University and in 1945 became Assistant Professor of Pharmacology at the University of Utah.

The Ciba Award is limited to men not over 35 years old and is given for meritorious accomplishment in the field of clinical or pre-clinical endo-

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